ANNALS OF
INTERNAL MEDICINE

VOLUME 9 MARCH, 1936 NUMBER 9

LONG-STANDING CASES OF AURICULAR FIBRILLATION WITH ORGANIC HEART DISEASE; SOME CLINICAL CONSIDERATIONS *

By WILLIAM A. EVANS, M.D., F.A.C.P., *Boston, Massachusetts*

THE onset of auricular fibrillation is generally considered an unfavorable event in the course of organic heart disease. The reports in the literature indicate that the average duration of life after the onset of fibrillation is a matter of a few years comparable to that following the onset of malignant neoplastic disease. White [1] gives two to three years as the average duration. Of a group of 173 fatal cases Willius [2] found the average duration one year and three months. In 20 cases of auricular fibrillation associated with rheumatic heart disease Jones [3] found an average duration of three years and six months. Clerc and Stieffel [4] observed 54 per cent of their cases living a year or more and only 9 per cent over three years. Frick and Kennicott [5] reported an average duration of five years and eight months in a group of cases observed to exitus, while Cookson's [6] averages are five and one-fourth years for the rheumatic group and seven years in the non-rheumatic group. Thus in the more recent studies with perhaps longer periods of observation the outlook in auricular fibrillation appears to be more favorable. A few isolated instances of auricular fibrillation of unusually long duration have been reported. The longest is that of Heitz,[7] a case of non-valvular heart disease with fibrillation observed over a period of 32 years. He also reports two cases of 10 and 12 years' duration. Vaquez [8] observed a case for 12 years. Laslett's [9] report is of a case of 15 years' duration, and he mentions a case of Cowan's surviving almost 12 years. In the group studied by Frick and Kennicott, instances of fibrillation observed for 20, 16, 15, 13 and 12 years are recorded.

The purpose of the present study was to analyze a group of cases of organic heart disease known to have persistent auricular fibrillation for a long period of time and to determine what features may have contributed to their longevity. Cases of transient auricular fibrillation were excluded. From the records of the Peter Bent Brigham Hospital and of the private

* Received for publication September 5, 1935.
From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Massachusetts.

practice of S. A. Levine of Boston, 39 such cases were collected. The duration was regarded as being from the time at which auricular fibrillation was first recognized clinically until the time the patient was last seen. Inasmuch as in many instances the onset of auricular fibrillation must have antedated by years or months the time of clinical recognition and inasmuch as 26 or two-thirds of the cases are known to be still alive, the actual duration must be really much longer. Ten in the group are known to be dead and three are lost. At the time of onset the diagnosis was usually confirmed by the electrocardiogram, but in a few instances the diagnosis was considered to be established with certainty when made by a number of observers at different times clinically. In this group the duration of observed fibrillation was at least 8 years, the upper limit being three cases of 15, 17, and 18 years respectively, and the average duration for the whole group 10.3 years. The average duration in the rheumatic group was 10.0 years, as compared with 10.6 in the non-rheumatic group.

Sex

The sex incidence in the whole group was not remarkable, there being 22 males and 17 females, or 56 per cent and 44 per cent, respectively. In the rheumatic group there was a predominance of females (41 per cent versus 59 per cent); while in the non-rheumatic group there was a predominance of males (76 per cent versus 24 per cent). The slight predominance of males is quite similar to that found by Lewis,[10] Willius,[2] Brachman [11] and Mohler and Lintgen [12] in unselected groups of cases with auricular fibrillation. Campbell [13] and Levine [14] observed an equal distribution, and White [15] a slight predominance of females, while Cookson [6] in a large group found twice as many females as males.

Age

There have been many reports of the age incidence in auricular fibrillation and eight of these have been charted (figure 1). There is the same

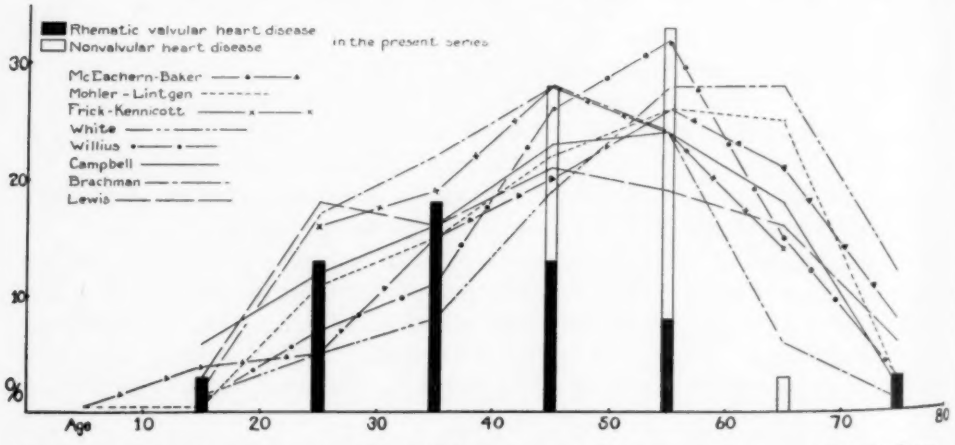

FIG. 1. Age incidence in auricular fibrillation of unselected groups of cases obtained from the literature compared with the age incidence in this series of long-standing fibrillation.

general shape and character to these curves, and they offer a satisfactory standard for comparison with our group. Here the age taken was that at the time at which auricular fibrillation was first recognized. It is apparent that the cases of long duration may occur at about any age but that they are most common in the fifth and sixth decades as with unselected cases of auricular fibrillation. The close agreement of the curves indicates that the age of the patient at the time of onset has little to do with the prognosis. When the valvular and non-valvular cases are analyzed separately, slight differences are detected which may have significance, and this will be discussed below.

Incidence of Associated Heart Disease

A number of reports on the incidence of associated heart disease are available, and these have been tabulated for comparison. (Table 1.) Here

Table I

Type of Heart Disease Associated with Auricular Fibrillation

Authors	Number of Cases	Rheumatic Heart Disease per cent	Non-Rheumatic Heart Disease per cent				
			Arterio-sclerotic	Hyper-tensive	Thyroid	Syphilitic	Unclassi-fied
Mohler, Lintgen [12]	220	42	32		4.6	1.4	20
Levin [22]	33	64	15		9	3	9
Clerc, Stieffel [4]	75	65					
Coffen [15]	37	62					38
Campbell [13]	100	53	36		11		
Brachman [11]	359	62	32		3	2	
Levine [14]	128	36	31				34
Cookson [6]	361	69	22		7	2	
Stroud, Laplace, Reisinger [20]	253	48	35		4	9	4
McEachern, Baker [16]	575	34	31	17	8	3	7
Frick, Kennicott [5]	51	49					51
Yater [21]	145	20		8	44	1	27
Lewis [10]	141	54					46
Willius [2]	500	31		20	33		16

the agreement is not so satisfactory, partly because of different terminology and criteria for diagnosis, partly because of the variable incidence of such diseases as rheumatic fever and toxic goiter in different localities and possibly also because of a greater interest in certain types of disease in different institutions. However, certain general features are available for comparison.

Rheumatic heart disease occurred in 22, or 54 per cent, of our group, a figure one might reasonably expect to find in an unselected group. A diagnosis of mitral stenosis was made in all of the 22 cases. An additional

diagnosis of aortic insufficiency was made in six, two of which also had aortic stenosis. There is nothing peculiar about this distribution which would help in basing the prognosis on the kind of valve lesion. The average age of the patients at the time of onset of auricular fibrillation in this rheumatic group was 39.7 years. This compares with an average of 37 years found by Levine [14] in a comparable group. This supports the view that in rheumatic heart disease auricular fibrillation is less serious if it occurs in older rather than in younger individuals.

Syphilitic heart disease is very rarely associated with auricular fibrillation, and it is not surprising that no instance of that type of heart disease appeared in our series. In the 31 cases in which the Wassermann test was carried out it was reported negative.

Hyperthyroidism was present at the time auricular fibrillation was recognized in two of the cases. However, the fact that fibrillation persisted after thyroidectomy and a restoration of the basal metabolism to normal limits would indicate that the hyperthyroid state was not alone responsible for the irregularity. Indeed one of the cases had rheumatic heart disease with mitral stenosis, and the other was approaching the older age group with a large heart, the enlargement being confirmed roentgenologically, when auricular fibrillation and hyperthyroidism were first recognized. In such a series one would not expect to find fibrillation of long duration associated with hyperthyroidism without underlying organic heart disease as well.

Non-Valvular Heart Disease. Our series contains 17, or 44 per cent, of such cases, five of which (13 per cent of the total) might be considered to have hypertensive heart disease. The relative incidence of hypertensive heart disease was higher in the comparable studies of McEachern and Baker [16] and Willius [2] so that hypertension would appear to be a somewhat unfavorable factor in this group. The average age at the onset of fibrillation in this group was 50.4 years, which is significantly less than the average of 58 years found by Levine [14] in a comparable group of undetermined duration. Thus, here in contrast with the rheumatic group, the duration of life following the onset of fibrillation is longer in the relatively younger patients. Therefore, it seems that in the group studied there is a difference of about 10 years between the age of onset of fibrillation in valvular and non-valvular cases (39 years and 50 years), as compared with a difference of about 20 years in the two groups of unselected fibrillators.

Status of the Heart and Circulation at the Onset of Auricular Fibrillation

Heart Size. It is generally accepted that a large heart indicates a poor prognosis. However, in this series the examination at the onset of fibrillation indicated some degree of enlargement in 32 instances, and in the others it may have been present but not recognized. In 19 instances the enlargement was marked and in five of these this was confirmed roentgenologically.

Hypertension. At the outset of this study it was thought that evidence might be found showing that the presence of hypertension exerted a favorable influence on the course of mitral stenosis (Levine and Fulton [17]). However, the data seemed to be too meager either to prove or disprove this conception. Of the 22 rheumatic valvular cases, only two were observed to have a systolic arterial tension above 150 mm. of mercury during the entire period of observation. Furthermore, the average blood pressure for the various decades as observed at the onset of fibrillation follows more closely the normal curve than that found by Levine and Fulton for mitral stenosis. However, a number of our patients developed increasing pressures during the period of observation, five of them reaching pressures above 150. Thus, with seven of the 22 patients having or acquiring pressures above 150, it appeared that hypertension was a little more prevalent in the valvular group (average age 38.7 years) than one might have expected in the average population of the same age period.

Of the 17 patients with non-valvular heart disease five had hypertension when first seen at the onset of fibrillation and in two hypertension developed.

Objective Signs of Congestive Failure. Persistent râles at the lung bases, enlargement of the liver or peripheral edema was noted in 16 cases at the onset of fibrillation. In 19, no objective evidences of congestive failure were demonstrable although in some of these there was dyspnea and limitation of normal activity and later the development of congestive failure. This compares with Campbell's [13] observation that signs of failure are present in about one-half the cases of auricular fibrillation when seen for the first time. Three cases were very striking in having greatly enlarged hearts and marked signs of congestive failure when first seen, two of whom are still living after being followed for nine years and the other having been lost eight years after the onset of fibrillation.

Ectopic Beats. A few cases in this series were observed in the period just preceding the onset of fibrillation and they commonly had numerous premature beats. Occasionally these beats were so numerous that differentiation from auricular fibrillation could only be made electrocardiographically. According to White,[1] Willius,[2] Coffen,[18] and also Clerc and Stieffel,[4] extrasystoles associated with fibrillation indicate a poor prognosis. In this series, however, five cases were encountered in which the initial electrocardiogram showed premature ventricular beats as well as fibrillation. Thus their presence cannot be taken to indicate necessarily an unfavorable outlook. Apart from evidences of right or left ventricular preponderance no other electrocardiographic anomalies were encountered in the initial tracings.

Discussion

It is apparent that no clues to prognosis are offered by the evidence here analyzed. From data obtainable upon examination of a patient at the inception of auricular fibrillation it would seem impossible to predict his life

expectancy in any but the most general way. The most important factor in his longevity is perhaps his good fortune in escaping the serious accidents of the type of heart disease from which he is suffering. In the rheumatic patient with auricular fibrillation the most common cause of death after congestive failure is embolism and pulmonary infarction (Laws and Levine [19]). Another frequent cause of death in the patient with rheumatic heart disease is subacute bacterial endocarditis, but it is well known that this is very rare in auricular fibrillation, and there was no instance of it in our series. At least one episode of embolism was noted in 10 of our patients during the period of observation, and many survived a number of embolic phenomena in various organs. In the older age group death is commonly brought on by the vascular accidents of hypertension and coronary artery disease. Coronary thrombosis is recognized as rare in the presence of fibrillation and was observed in only one of our patients during the period of observation. However, two others were known to have survived attacks at or prior to the onset of fibrillation. One patient survived a cerebral vascular accident associated with hypertension. In contrast to the rheumatic group there was a conspicuous rarity of embolic phenomena.

Conclusions

1. A study was made of a group of 39 patients with organic heart disease who were known to have had auricular fibrillation for long periods of time ranging from 8 to 18 years.

2. Of these 39 cases there were 22 with rheumatic valvular and 17 with non-valvular heart disease. There were no cases of syphilitic or thyroid heart disease.

3. There was a predominance of females in the valvular group and of males in the non-valvular group.

4. Cases were encountered in all decades from the second to the eighth inclusive. The age distribution was quite similar to that of unselected groups reported in the literature except for a slight tendency to an increased predominance of cases in the fifth and sixth decades at the expense of the seventh and eighth decades. The average age in the rheumatic valvular group was slightly older and in the non-valvular group slightly younger than in comparable unselected groups.

5. Hypertension appeared to be slightly more common in the rheumatic valvular group and slightly less common in the non-valvular group than one would expect in the comparable groups of undetermined duration.

6. The majority of the patients had enlarged hearts, some to an extreme degree, at the onset of fibrillation, and almost half had objective manifestations of congestive failure when first seen.

7. It is believed that these patients owe their longevity in large part to their good fortune in escaping or surviving the accidents to which patients

with cardiac disease in general are subject, namely embolism, subacute bacterial endocarditis, cerebral hemorrhage and coronary thrombosis.

It is a pleasure to acknowledge the suggestions and criticisms of Dr. S. A. Levine.

BIBLIOGRAPHY

1. White, P. D.: Prognosis in heart disease in relation to auricular fibrillation and alternation of the pulse, Am. Jr. Med. Sci., 1919, clvii, 5.
2. Willius, F. A.: Auricular fibrillation and life expectancy, Minn. Med., 1920, iii, 365.
3. Jones, H. W.: Some points in the prognosis of auricular fibrillation, Lancet, 1926, ii, 640.
4. Clerc, A., and Stieffel, R.: Pronostic de l'arythmie complete, Bull. et mem. Soc. méd. d. hôp. d. Paris, 1927, li, 1139.
5. Frick, D. J., and Kennicott, R. H.: Auricular fibrillation; a review of a series of cases, Calif. and West. Med., 1928, xxviii, 779.
6. Cookson, H.: The etiology and prognosis of auricular fibrillation, Quart. Jr. Med., 1929–30, xxiii, 309.
7. Heitz, J.: Un cas d'arthymie complete permanente evoluant depuis trente-deux ans, Arch. d. mal. d. coeur, 1914, vii, 116.
8. Vaquez: Quoted by Heitz.[7]
9. Laslett, E. E.: A case of auricular fibrillation of 15 years' duration, Lancet, 1927, i, 1290.
10. Lewis, T.: Clinical disorders of the heart beat, 6 Ed., 1925, Shaw and Sons, London.
11. Brachman, D. S.: Auricular fibrillation, Lancet, 1921, i, 374.
12. Mohler, H. K., and Lintgen, C.: Auricular fibrillation, Penn. Med. Jr., 1931, xxxv, 68.
13. Campbell, M.: The etiology of auricular fibrillation, Guy's Hosp. Rep., 1929, lxxix, 261.
14. Levine, S. A.: Auricular fibrillation: some clinical considerations, Am. Jr. Med. Sci., 1917, cliv, 43.
15. White, P. D.: Observations on functional disorders of the heart, Am. Heart Jr., 1926, i, 527.
16. McEachern, D., and Baker, B. M.: Auricular fibrillation, Am. Jr. Med. Sci., 1932, clxxxiii, 35.
17. Levine, S. A., and Fulton, M. N.: The relation of hypertension to mitral stenosis, Am. Jr. Med. Sci., 1928, clxxvi, 465.
18. Coffen, T. H.: The favorable prognosis of auricular fibrillation, Jr. Am. Med. Assoc., 1923, lxxxi, 440.
19. Laws, C. L., and Levine, S. A.: Clinical notes on rheumatic heart disease with special reference to the cause of death, Am. Jr. Med. Sci., 1933, clxxxvi, 833.
20. Stroud, W. D., Laplace, L. B., and Reisinger, J. A.: The etiology, prognosis, and treatment of auricular fibrillation, Am. Jr. Med. Sci., 1932, clxxxiii, 48.
21. Yater, W. M.: Pathologic changes in auricular fibrillation and in allied arrhythmias, Arch. Int. Med., 1929, xliii, 808.
22. Levin, L.: Auricular fibrillation: prognostic criteria, Jr. Med. Soc. N. J., 1930, xxvii, 514.

THE ETIOLOGY OF ABDOMINAL PAIN IN DIABETIC ACIDOSIS *

By HARRY WALKER, M.D., *Richmond, Virginia*

THE usual signs, symptoms, and laboratory findings in prediabetic coma are well known. The clinical picture of dehydration associated with malnutrition, polyuria, and odor of acetone on the breath, decreased intraocular tension, and Kussmaul breathing, when found in conjunction with sugar and acetone bodies in the urine make a clinical picture that could hardly be confused with any other condition. Other laboratory findings are a high blood sugar, a low CO_2 combining power of the blood plasma, and leukocytosis. The white cell count sometimes rises above 65,000 [1] per cubic millimeter of blood.

This picture is usually clear cut and offers no difficulty in diagnosis. There are, however, exceptions to this rule; in fact, the picture is occasionally complicated by symptoms and signs referable to the abdomen which may make it difficult or impossible to determine whether the patient has an intra-abdominal surgical lesion, or whether the symptom complex from which the patient is suffering is due entirely to acidosis. Obviously, it is of primary importance promptly to make a differential diagnosis. To subject a patient on the verge of diabetic coma to an emergency surgical operation is never wise unless a true emergency exists; on the other hand, to delay too long an operation in a diabetic that needs emergency surgery is equally unwise.

The following is a case report of this complex syndrome, presenting an excellent example of the difficulty in diagnosis that some of these patients present when first seen.

CASE REPORT

J. B., male, aged 17, admitted to Memorial Hospital March 25, 1933.

The patient, a known diabetic for two years, was discharged from this hospital on November 10, 1932, following treatment for an early diabetic coma. At the time of his dismissal the patient was placed on a diet with 225 grams of carbohydrate, 80 grams of protein, and 60 grams of fat together with 20 units of insulin three times a day before meals. The patient progressed well on this treatment and was followed in the Out-Patient Department weekly. He followed his instructions faithfully until seven days before admission. At this time his supply of insulin became low and he took only 15 units each day instead of his usual 60 units. On the day before admission he did not eat as much as usual and took only 10 units of insulin, before breakfast. On the day of admission he ate practically nothing. The patient went to bed feeling very well but awoke in the early part of the night (about 1:00 a.m.) nauseated. He continued to be nauseated throughout the night but did not vomit until the following morning at about 8:00 a.m. He continued to vomit throughout the day, vomiting every five to 10 minutes. After each attack of vomiting the

* Received for publication October 21, 1935.
From the Department of Medicine, Medical College of Virginia.

patient would drink a large quantity of water. About 1:00 p.m. the patient began having a sharp pain in the epigastrium just to the left of the mid-line. The pain increased in severity, was sharp and shooting in character, soon extending over the entire abdomen and radiating up the chest as high as the supra-sternal notch. The pain was increased by deep respiration. Nausea, vomiting, and constant pain continued, all increasing in severity. At about 4:00 p.m. the patient's mother gave him 40 units of insulin which seemed to have no effect on either the vomiting or pain. All during the day and the night before the patient had passed large amounts of urine, much more than usual. At 6:00 p.m. the patient was admitted to the hospital.

Physical examination at that time revealed a much dehydrated white boy in agonizing pain. The respiration was shallow. Examination of the head and neck showed nothing unusual. The heart rate was 100 and the blood pressure 120 mm. of mercury systolic and 80 diastolic. There was no evidence of cardiac enlargement and no murmurs were present. The lungs were clear. The abdomen was rigid, board-like in character, giving one the impression that one was dealing with a perforated peptic ulcer or some other emergency surgical condition. There was a slight infection of the terminal phalanx of the left thumb. The remainder of the examination was negative.

The laboratory reports were as follows: Urine, amber, clear, acid, specific gravity 1.025, heavy trace of albumin, sugar four plus, acetone four plus, diacetic acid two plus. Red blood count 5,160,000; hemoglobin 95 per cent; white blood count 26,600; 87 per cent polymorphonuclears; 11 per cent lymphocytes; and 2 per cent eosinophiles. The blood sugar was 444; and the plasma CO_2 was 20.2 volumes per cent.

Immediately after admission the patient was given 50 units of insulin, hypodermically, and 1,000 c.c. of normal saline were given by vein. The abdominal pain immediately began to lessen in severity and within 45 minutes the pain had completely subsided and the abdomen had become soft. At this time the blood sugar was repeated and was found to be 380 mg. per 100 c.c. of blood; the CO_2 was 22; the urine was still positive for sugar, acetone, and diacetic acid.

Confronted with a situation of this kind, how can a differential diagnosis be made? The answer cannot be given without making qualifications. Literature concerning this condition is scarce; however, McKittrick [2] in a somewhat recent review suggests the following observations as useful. First, he (McKittrick) states in his review of patients who had been operated on and no surgical lesion found, that these patients before operation always suggested some wide-spread abdominal pathologic process as the cause of the abdominal findings. Second, that in diabetic coma, vomiting usually precedes pain; while in pre-coma cases with surgical complications, pain usually precedes vomiting—particularly is this true in acute appendicitis. Third, when appropriate therapy is applied, the signs and symptoms due to acidosis clear up promptly; while, of course, the signs and symptoms in the surgical cases will usually progress. He further states that differentiation is not always possible and, when the patient does not respond in a reasonable length of time, an exploratory laparotomy should be done.

The etiology of this interesting condition has never been satisfactorily explained. Various possibilities, of course, have been suggested and explored. Dilatation of the stomach has been offered as a possible cause; but it is common knowledge that gastric dilatation does not produce a true spasm of the abdominal muscles. It, of course, does produce discomfort

in the abdomen, but rarely if ever agonizing pain. Hepatic engorgement has also been suggested as an explanation, but here again engorgement of the liver as we see it clinically never produces a syndrome comparable to that seen in the case reported here. That the abdominal symptoms in diabetic acidosis could be due to a surgical lesion is ruled out by the fact that recovery is too prompt. In addition to this fact, exploration fails to find sufficient incriminating evidence against any abdominal organ to account for the clinical findings; and the same may be said of autopsy findings in these cases. Neither does dehydration explain all of the facts since it is a routine finding in pre-coma cases, and yet, certainly the majority of even markedly dehydrated patients present no abdominal signs or symptoms. Then again dehydration when found in other clinical conditions does not produce the findings reported here.

It is always dangerous to draw conclusions from one case, yet, in the case history here reported several things stand out. First, the vomiting preceded the pain by several hours; second, the patient received insulin in large amounts before entering the hospital, yet, in an insufficient quantity to control the acidosis; third, prompt relief followed the administration of a small quantity of normal physiological salt solution; fourth, the patient continued to show evidence of acidosis after the pain had subsided. These facts suggest that acidosis was not solely responsible for the symptoms since, when measured by laboratory means, there was no reduction. The history suggests too that insulin was certainly not the sole factor in controlling the symptoms in this case, but rather that the salt solution was responsible for the relief of symptoms. When one thinks of other clinical conditions such as heat cramps and "gastric tetany," the connection seems even more probable.

Heat cramps, a condition described by Edsall,[3] is commonly seen in the South, especially in the summer months in those who do manual labor while exposed to the sun or high temperatures. It is well established that this condition is in some way associated with chloride deficiency and is brought about by loss of chlorides, chiefly through perspiration. Salt solution not only promptly controls the symptoms but prevents them. It might be added that the pain in this condition is so severe that it does not readily yield to moderate, or for that matter, sometimes even to large doses of morphine sulphate.

A review of some of the facts known about "gastric tetany" associated with pyloric obstruction makes this explanation even more plausible. Here the patient loses his chlorides by vomiting and not only does abdominal pain follow but so does violent pain in any group of muscles that are vigorously exercised. In view of these facts, it is suggested that the chain of events producing abdominal symptoms in diabetic acidosis probably develops in this order. First, because of improper fat oxidation, acidosis develops; the acidosis in susceptible patients causes vomiting; the acidosis not being controlled, the vomiting continues. Second, the continuous vomiting depletes

the body of chlorides because of loss of hydrochloric acid. The excessive diuresis would produce further chloride loss. Third, in the exercise of abdominal muscles and muscles of respiration, there is brought about a condition in these muscles similar to that which is present in heat cramps and "gastric tetany"; hence, the pain, and hence the relief by sodium chloride.

It is regretted that no blood chloride determinations were made on this patient. However, it must be remembered that, when marked dehydration of the body is present, a determination of the plasma chlorides is not a true index of the total body chlorides. In fact, plasma chlorides may remain normal while the chloride content of the body as a whole may be markedly reduced. The chlorides in "gastric tetany," of course, are always low but in heat cramps this is not the case. In fact, chloride determinations were made on the blood plasma of eight patients admitted to our medical wards during the past summer, and in only two of them were the chlorides decreased and in those very slightly. That there is certainly depletion of the body chlorides in diabetic acidosis is a known fact. Peters and Van Slyke [4] state that the depletion may be brought about in several ways, namely, vomiting, diuresis, and the displacement of chlorine by oxybutyrate anions, the displaced chlorine being excreted as ammonium chloride. Certainly, if this patient's plasma chlorides had been normal, it would not have thrown any light on the total body chlorides and would be no argument against the explanation for his pain given here.

Conclusions

A patient with diabetic acidosis and associated abdominal symptoms is reported. A review of the history and the prompt relief which followed the administration of sodium chloride suggest that the abdominal pain present in this condition may be associated with depletion of body chlorides.

BIBLIOGRAPHY

1. Allan, F. N.: Diabetic acidosis and leukocytosis, Am. Jr. Med. Sci., 1923, vii, 641–645.
2. McKittrick, L. S.: Abdominal symptoms with and without abdominal lesions in diabetic acidosis, New Eng. Jr. Med., 1933, ccix, 1033–1036.
3. Edsall, D. L.: Two cases of violent but transitory myokymia and myotonia apparently due to excessive hot weather, Am. Jr. Med. Sci., cxxvii, 1904, 1003–1011.
4. Peters, J. P., and Van Slyke, D. D.: Quantitative clinical chemistry, I, 1931, The Williams and Wilkins Co., 1054–1055.

INTENSIVE LIVER THERAPY IN SPRUE *

By PHILIP CORR, M.D., F.A.C.P., *Riverside, California*

A recent report by Rhoads and Miller [1] indicates that adequate liver therapy is as satisfactory in sprue as it is in the somewhat related condition of pernicious anemia. These excellent results with liver therapy have stimulated an increase in the recognition of nontropical cases of sprue which are often reported as cases of chronic idiopathic steatorrhea. Mackie,[2] in July 1933, was able to find only 28 unquestioned cases of nontropical sprue and he added one of his own. Increased recognition of cases is evidenced by the fact that by March 1935 Snell [3] was able to state that there were well over 100 nontropical sprue cases on record. He further stated that 15 cases had been seen at the Mayo Clinic since 1927 with about half of them having been studied during the previous year.

The diagnosis of sprue is made on the basis of finding excess fat in the stools after a history is obtained of gaseous indigestion with marked loss of weight and weakness associated with chronic recurring diarrhea of watery, bulky stools. Intermittent sore mouth and tongue, latent or active tetany, amenorrhea, and an inanition edema are common symptoms in the more advanced cases. Emaciation with a distended abdomen is often striking. Laboratory findings, in addition to the excess fat seen macroscopically and microscopically in the pale, voluminous, foul stools, include the finding of a hypochromic or macrocytic anemia, hypocalcemia, and a decrease in the serum proteins. The roentgenologic findings include osteoporosis and osteomalacia in the advanced cases. Dilatation and redundancy of the colon have been commonly observed. Recently Camp [4] has described dilatation of the duodenum and a smoothing out of the irregular shadows of the valvulae conniventes and a clumping of the barium in smooth sausage-like masses in the jejunum and ileum.

Pancreatogenic steatorrhea differs from the steatorrhea of sprue in that the fault is in the decrease or lack of the external pancreatic secretion, and there is no fault in the absorptive power of the intestine. A much higher azotorrhea may be observed in pancreatic disease.[5] The frequently associated diabetes and the lack of concomitant sprue symptoms resulting from faulty absorption and atony of the intestines usually point to the correct diagnosis of pancreatic difficulty.

Pernicious anemia is characterized by lack of intrinsic factor [6] with the resultant principal effect upon the hematopoietic system without prominent bowel physiology disturbance. The rather constant presence of free hydrochloric acid in the gastric contents in sprue is a distinct aid in the differential diagnosis.

Pellagra is differentiated at times with great difficulty particularly in the

* Received for publication October 10, 1935.

early cases. The skin lesions and the mental symptoms are particularly helpful in the diagnosis of pellagra. Fortunately the treatment in the two conditions is about the same.[7]

The etiology of sprue is debatable but all students agree that there is a dietary deficiency factor. It is generally felt that in spite of Ashford's [8] work *Monilia albicans* is usually only a secondary invader [2] which causes much of the frothiness of the stool so often described in tropical cases. This dietary deficiency consists in a lack of an extrinsic factor in the food closely associated, if not identical, with the extrinsic factor of Castle. This lack, perhaps associated with a deficiency or lack of the intrinsic factor in some cases,[9] brings about the pathology in the small bowel which interferes with the absorption of the hematopoietic substance, fats, and to a lesser extent other food elements.

There is no agreement about a characteristic underlying pathology. Marked reduction to complete absence of fat in the body and a liver considerably reduced in size are the constant evidences of starvation. Reduction in the size of the heart is common from the same cause. It has been felt that the essential lesion is an atrophic enteritis with patchy, transient, inflammatory lesions not always present at autopsy.[10] This may account for the widely divergent autopsy findings noted in the gastrointestinal tract in sprue. Fatal perforation has occurred in the cecum from thinning of the wall.[11] A gastro-jejuno-colic fistula has caused sprue-like symptoms,[12] but an extensive chronic ulcerative enteritis seen one year ago did not have sprue-like symptoms.[13] The most careful work on the bone marrow evidences that sprue in this respect simulates pernicious anemia.[14] Roentgenologic evidence indicates that there is an edema as well as atony in the intestinal tract.[3]

Manson-Bahr [15] was perhaps wise in saying that nontropical sprue cases in order to be diagnosed as such should present the typical diarrhea, flatulency, anemia, mouth symptoms and the characteristic response to appropriate treatment.

The following recently observed typical case of sprue is presented as a basis for emphasis of many of the interesting features of this symptom syndrome, particularly as to its treatment.

Case Report

History. K. K., an American woman aged 49 years, for 12 years a resident of Havana, Cuba, was first seen in consultation with Dr. Bon O. Adams, March 29, 1935. Except for an increasing lassitude which had been present since 1925 she was active and in good health until January 1932 when, for the lassitude, she had all her teeth removed. Sore mouth followed and was present intermittently since the alveolectomy. The sore mouth was troublesome enough for her to get three complete sets of dentures without lasting satisfaction from any of them. Anorexia had been prominent and persistent since the onset of the sore mouth and tongue. The weight dropped from 135 pounds in January 1932 to 69 pounds in November 1934. Since November she had not been weighed, but an increasing edema, which had been transiently present several months before, had increased her weight to a probable 110 or more pounds. Weakness had become so severe that she could barely turn

over in bed unaided. Since the onset of her trouble in 1932 she had a painless, watery, bulky but not foamy diarrhea with passage on an average of three to four stools daily, the number varying from one to nine. Usually there would be three or four stools early in the morning and occasionally a stool before meals when there was an exacerbation. In spite of this copious diarrhea the gaseous distention was so marked that enemas were required twice daily to keep her comfortable. The menses had ceased in 1931 when the patient was 45 years of age. Intermittent and rather marked tingling of the finger tips had been noted for several months.

For a period of 10 months before November 1934 the patient had been carefully and competently studied in the middle west. No diagnosis had been made, but the letters of information she carried with her evidenced that anorexia nervosa was considered to be the most likely explanation of her difficulties. During their observation the hemoglobin dropped from 89 to 50 per cent and the erythrocytes dropped from 3,200,000 to 2,010,000 in spite of temporary improvement from blood transfusions. The leukocytes had dropped from 6,500 with 47 per cent neutrophiles, to 3,100 with 47 per cent neutrophiles. This macrocytic anemia was accompanied by 13° of free hydrochloric acid in the gastric contents. Stools for blood, parasites and ova; a Kahn test; a basal metabolic rate: liver function tests using both the galactose tolerance and the dye methods; and repeated roentgenologic gastrointestinal examinations were reported as normal. Their therapy had included forced feeding to overcome the effects of previous inadequate protein intake, and a period of intramuscular liver extract therapy which failed to bring about satisfactory hematopoietic response. For some months the patient had been taking six capsules of liver extract (Extralin) and pancreatic extract (Pankreon).

Examination revealed extreme weakness with an extreme degree of edema of the legs and of the abdominal wall, with moderate edema of the arms and face. Fluid was definitely present in the abdomen. The blood pressure was 78/62 with a pulse of 80 and a temperature of 97.8°. The tongue was pinkish-red and atrophic with almost complete absence of papillae. Trousseau's sign was definitely positive.

The stools contained an excessive amount of fat macroscopically and microscopically. Cultures of two stools failed to grow Monilia. The hemoglobin was 43 per cent (Sahli) with 1,330,000 red blood cells and a color index of 1.6. The leukocytes numbered 3,000 with 51 per cent neutrophiles. The urine contained a trace of albumin. The blood urea was 10 mg. per 100 c.c.

On the basis of this typical history and the confirmatory findings, a diagnosis of sprue was made. It was felt that previous liver therapy had been inadequate. Beginning April 1, 1935 daily intravenous injections of 20 c.c. of liver extract (Parke-Davis & Co.) were given for 12 days. This was followed by 16 similar injections given every second day, following which the intervals between injections were gradually lengthened. By September they were being given twice monthly.

The diarrhea promptly stopped after the first injection of liver extract, but for five days there was no other sign of improvement, the patient appearing almost moribund. Severe tetany developed after giving pitressin to relieve the gaseous distress in the abdomen. The use of the tourniquet for the intravenous therapy consistently produced annoying, typical carpal spasms. The blood calcium on April 9 was 7.5 mg. and the blood phosphorus 3.5 mg. per 100 c.c.

Beginning with the sixth day of treatment, improvement in the general condition was dramatic and continuous. By the twelfth day the appetite was ravenous, the patient could sit up in bed with energy to spare, the gaseous distention was much improved, and the tetany had almost disappeared. Vitamin D and calcium was started a few days after improvement in the tetany had begun. The weight was 63 pounds after two weeks of excessive eating but by that time the edema had practically disappeared. Subsequently there was a steady increase in weight so that by September the weight had reached a level at 120 pounds. The sore mouth disap-

peared with the beginning of the improvement in April and has not recurred. The tongue appears to be normal. Nor has there been any return of tetany. By June 4 the blood calcium was 10.5 mg. per 100 c.c. The appetite remained a ravenous one until about the middle of August since which time it has been normal. Bowel movements for months have been normal with one movement daily. The stools are not bulky and microscopically there is no excess fat. The abdomen is not distended nor has there been any gaseous indigestion the past several weeks. The patient enjoys a normally active life. There is still a small amount of edema of the ankles which disappears overnight. On June 3 the serum albumin was 3.9 per cent and the serum globulin 2.1 per cent. At that time being up and around a very little resulted in a rather marked leg edema. On September 25 the serum albumin was raised to 5.1 per cent and the serum globulin was 1.3 per cent. It was felt that the inanition edema was increased by a weakness of the heart muscle from starvation in spite of the rise of the blood pressure to 122 mm. mercury systolic and 74 diastolic, a rise which has persisted up to the last examination.

The response of the blood was at first satisfactory although it was not remarkable in view of the considerable amount of parenteral liver given. The reticulocytes rose only to 4 per cent. After the initial rise to 59 per cent hemoglobin with a 2,790,000 erythrocyte count on the twelfth day there was difficulty in improving the blood picture. On the twenty-ninth day the hemoglobin had dropped to 47 per cent with 2,710,000 red blood cells. By that time the patient could tolerate iron without added abdominal distress so one gram of ferrum reductum was added daily to the other therapy. This resulted by September 25 in a hemoglobin of 84 per cent (Dare) with 4,590,000 erythrocytes, a color index of 0.9, the white blood cells numbering 6,450 with 58 per cent neutrophiles, 39 per cent lymphocytes, 2 per cent monocytes and 1 per cent basophiles.

Characteristic roentgen-ray pathology was not disclosed in the gastrointestinal examination conducted after recovery from the severe symptoms had taken place.

Discussion

Although sprue is uncommon in Cuba [16] this case must be considered as one of the tropical variety in spite of the fact that no Monilia could be found in the stools.

While there may have been a dietary deficiency before 1932 there certainly was a dietary deficiency after the teeth were removed. The sore mouth of the alveolectomy shortly became the sore mouth of sprue. There ensued a functional as well as perhaps an anatomical interference with the absorption of fats and other food elements. Anorexia, weakness, emaciation, flatulent indigestion, and fatty, bulky diarrhea resulted. Inanition caused a severe edema, a marked drop in blood pressure and a cardiac weakness. The hypocalcemia is explained on the basis of faulty absorption and reabsorption of calcium in the bowel because of formation of calcium soaps with the excess fat in the intestine as well as by poor absorptive power of the small bowel due to edema, atony, and from possible inflammatory changes.

Faulty absorption as well as inadequate ingestion of iron is an important consideration. It has been found that it is often necessary to give large doses of iron in order to obtain satisfactory blood response.[9]

For many years bizarre diets, all more or less rich in the extrinsic factor, have been moderately successful in the treatment of sprue.[1] Reduction

of fats in the diet has always been stressed and was followed in the beginning in this case. Snell [8] emphasizes the use of vitamin D and calcium.

Since the introduction of the liver diet in the treatment of these cases by Bloomfield and Wyckoff [17] in 1927, liver therapy has been found to be most satisfactory, probably because it contains more of the extrinsic factor as well as the hematopoietic substance. However, it was found that faulty absorption occasionally prevented adequate utilization of the liver, and parenteral liver extract was then used. According to the experience of Rhoads and Miller [1] much more liver extract was necessary to control the sprue symptoms than is commonly necessary in pernicious anemia. Their report detailed four cases which had been treated previously with rather large doses of parenteral liver extract and which did not respond until daily doses such as were given in this case were administered.

Conclusion

A case of sprue is reported illustrating the effectiveness of liver therapy.

BIBLIOGRAPHY

1. Rhoads, C. P., and Miller, D. K.: Intensive liver extract therapy of sprue, Jr. Am. Med. Assoc., 1934, ciii, 387–391.
2. Mackie, T. T.: Nontropical sprue, Med. Clin. N. Am., 1933, xvii, 165–185.
3. Snell, A. M., Camp, J. D., and Watkins, C. H.: Nontropical sprue, Proc. Staff Meet. Mayo Clinic, 1935, x, 177–185.
4. Snell, A. M., and Camp, J. D.: Chronic idiopathic steatorrhea, Arch. Int. Med., 1934, liii, 615–630.
5. Comfort, M. W.: The diagnostic value of steatorrhea and azotorrhea in chronic pancreatitis, Med. Clin. N. Am., 1934, xviii, 519–529.
6. Sturgis, C. C., Isaacs, R., Goldhamer, M. S., Bethell, F. H., and Farrar, G. E.: Blood, Arch. Int. Med., 1935, lv, 1001–1081.
7. Spies, T. D.: The medical treatment of early pellagra, Jr. Am. Med. Assoc., 1935, cv, 1028.
8. Ashford, B. K.: Sprue (*in* Cecil's Textbook of medicine, 1933, 390–394, W. B. Saunders Company, Philadelphia).
9. Castle, W. B., and Rhoads, C. P.: The etiology and treatment of sprue in Puerto Rico, Lancet, 1932, i, 1198.
10. Fairley, N. H.: Sprue; its applied pathology, biochemistry, and treatment, Trans. Roy. Soc. Trop. Med. and Hyg., 1930, xxiv, 2.
11. Low, G. C., and Fairley, N. H.: Fatal perforation of the cecum in a case of sprue, Brit. Med. Jr., 1934, ii, 678–679.
12. Fairley, N. H., and Kelner, T. P.: Gastro-jejuno-colic fistula with megalocytic anemia simulating sprue, Brit. Med. Jr., 1931, ii, 1335–1341.
13. Corr, P., and Boeck, W. C.: Chronic ulcerative enteritis, Am. Jr. Dig. Dis. and Nutr., 1934, i, 161–164.
14. Rhoads, C. P., and Castle, W. B.: The pathology of the bone marrow in sprue anemia, Am. Jr. Path., 1933, 813–827.
15. Manson-Bahr, P.: On nontropical or indigenous sprue, Jr. Trop. Med. and Hyg., 1929, xxxii, 118, 119.
16. Agramonte, A.: Trans. Internat. Conference on health problems in tropical America, Kingston, Jamaica, 1924, p. 703, United Fruit Co., Boston.
17. Bloomfield, A. L., and Wyckoff, H. A.: Remission in sprue following a high liver diet, Calif. and West. Med., 1927, xxvii, 659–660.

LOCALIZATION OF THE SITE OF EXPERIMENTAL PREMATURE CONTRACTIONS AND BUNDLE BRANCH LESIONS BY MEANS OF MULTIPLANE CHEST LEADS *

By Joseph Weinstein, M.D., and David I. Abramson, M.D.,
Brooklyn, New York

In a recent publication,[1] the authors presented the results obtained in detecting and localizing experimental myocardial lesions by means of certain chest leads,[2] which differed in a number of respects from the others thus far employed. These experimental leads (designated as multiplane chest leads) consisted of combinations of linear electrodes placed on the anterior and posterior surfaces of the chest parallel to and beyond the estimated borders of the heart; in contra-distinction to the conventional chest leads, advocated by other investigators [3, 4, 5] in which at least one electrode of sufficiently large circumference was placed on the anterior or posterior chest wall directly over the heart itself. In our experimental leads a number of recording planes were employed, these appearing to be responsive to electrical changes of even small magnitude. It was found that superficial cauterization of various parts of the epicardial surface of both ventricles consistently produced RS–T changes in the experimental chest lead tracings, whereas in only one-half of these cases were similar alterations noted with the standard three leads, and in two-thirds with Lead IV. At the same time it was found that the experimental chest leads generally indicated the ventricle involved.

The present work was undertaken in order to investigate in more detail the question of the value of these leads in localization. It is the purpose of this communication to report the electrocardiographic alterations observed in the experimental chest lead tracings following first, the artificial production of premature contractions from various parts of the ventricles, and second, the transection of either one or the other branches of the Bundle of His.

Method

The experiments were performed on cats under "Dial" anesthesia (intraperitoneal). The German silver electrodes used in our previous experiments were replaced by ones of steel wire (1/32 inch in diameter), since polarization was less often present with the latter. The sites of insertion of the electrodes, as well as the manner in which the animal was prepared

* Received for publication May 30, 1935.

From the Department of Physiology and Pharmacology, Long Island College of Medicine; and from the Medical Service and Cardio-Vascular Laboratory of the Jewish Hospital of Brooklyn.

With the technical assistance of Pearl Kramer.

and the heart exposed, were similar in all respects to those used in the previous work.[1]

The following leads were employed (figure 1):

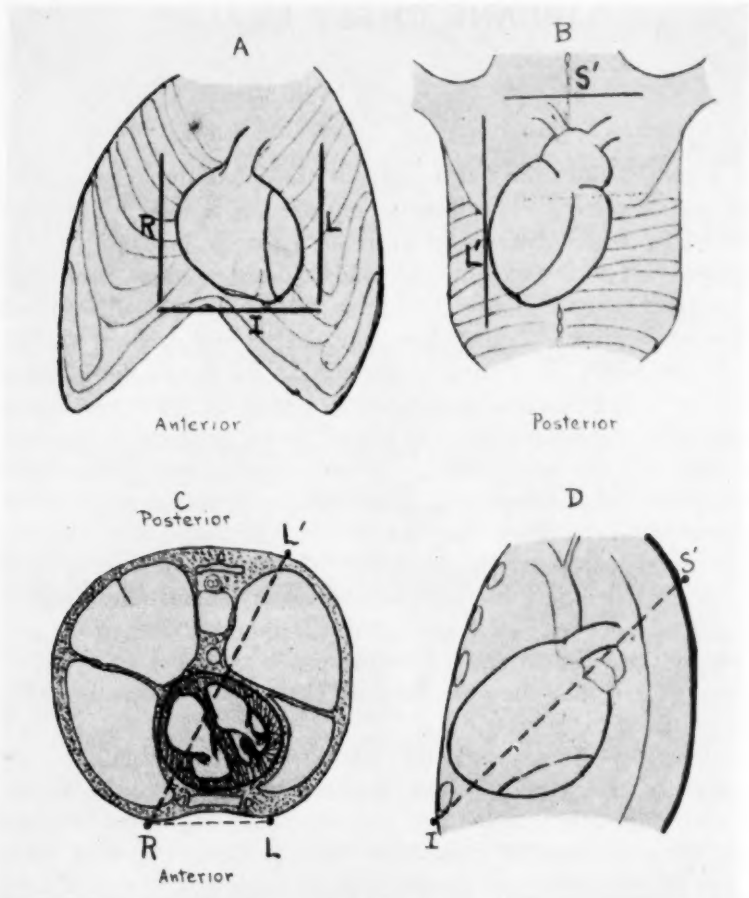

FIG. 1, *A* and *B*. Diagrammatic representation of the position of the experimental chest electrodes. *A*, Anterior surface. R, right electrode located some distance to the right of the sternum. L, left electrode, extending in the left anterior axillary line parallel to electrode R. I, inferior electrode, inserted somewhat above the level of the ensiform cartilage and extending across the chest. *B*. Posterior surface. S', superior posterior electrode, extending across the back at about the level of the superior border of the scapulae. L', left posterior electrode placed so as to correspond in position to L (left anterior electrode). *C* and *D*. Cross section and lateral view of chest illustrating the various electrode combinations. L'R, left posterior and right anterior electrodes. RL, right anterior and left anterior electrodes. S'I, superior posterior and inferior anterior electrodes.

1. L'R—(L') electrode placed on the posterior chest wall at the level of and grossly parallel to the left border of the heart and (R) electrode placed on the anterior chest wall at the level of and grossly parallel to the right border.

2. RL—Both electrodes placed on the anterior surface of the chest, one (R) at the level of and grossly parallel to the right border of the heart, and the other (L) at the level of and grossly parallel to the left border.
3. S′I—(S′) electrode placed at about the level of the spines of the scapulae on the posterior chest wall and extending practically across it, and (I) electrode situated at the level of and grossly parallel to the inferior border of the heart on the anterior chest wall and extending across it.

As in the former investigation, the electrodes were led to a selector switch by means of which any chosen pair could be connected to the standard Lead I contacts of the electrocardiograph. The posterior electrode in each combination was attached to the right arm lead wire of the galvanometer and the anterior electrode to the left arm wire. In the case of Lead RL, in which both electrodes were situated anteriorly, the right electrode was combined with the former and the left electrode with the latter.

The premature contractions were produced by stimulating the ventricles by means of induction shocks from an inductorium, the primary circuit of which was broken by the ordinary Harvard spring interruptor. The latter was so arranged that the number of stimuli per minute was about 10 or 15 in excess of the heart beat. Besides the experimental chest leads, the conventional three leads and Lead IV were generally obtained for each site of artificial impulse formation. In a number of experiments, after the extrasystoles were recorded, the heart was pulled and rotated either to the right or left by means of hooks inserted into the outer wall or by the gloved hand, and then another set of tracings taken under these conditions.

The branches of the Bundle of His were cut according to the method advocated by Roberts et al.[6] At the end of the experiments (12 in all) the hearts were examined grossly (and in two, histologically as well) for evidence of complete transection of the desired branch.

Localization of Site of Origin of Premature Ventricular Contractions by Means of the Experimental Chest Leads. Examination of table 1 and figure 2 reveals that consistently the main deflection in Lead RL was upwardly directed when premature contractions were produced from any part of the right ventricle, base or apex, anterior or posterior surface, and downwardly directed in the case of impulses arising from comparable spots on the left ventricle. In Lead L′R, the reverse was true; impulses arising from any portion of the right ventricle resulting in negative main deflections, whereas those from the left ventricle produced positive ones. Stimulation of the anterior and posterior aspects of the septum intervening between the outer walls of the ventricles gave variable types of changes in these leads. With Lead S′I, premature contractions originating from any part of the anterior surface of the heart, either right or left ventricle (with the exception of certain instances in the case of the left apex anteriorly), caused the

main wave to be upwardly directed, while stimulation of any portion of the posterior surface, either right or left ventricle, resulted in a negative main deflection. Impulses arising from the lateral surfaces of the right and left ventricles produced changes which fell into either one or the other category or contained characteristics of both. In other words, the main deflection

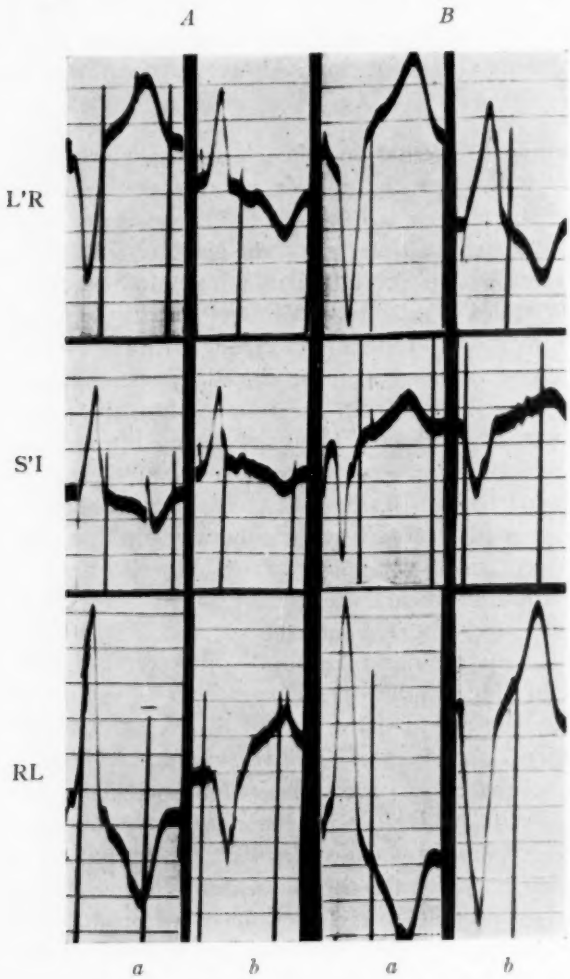

FIG. 2. Curves produced by stimulation of the ventricles. *A*. Stimulation of anterior surface of the heart; *a*. Right ventricle; *b*. Left ventricle. *B*. Stimulation of posterior surface of the heart; *a*. Right ventricle; *b*. Left ventricle.

in Lead S'I in cases of artificial stimulation from these sites was positive or negative, or both positive and negative. As regards the anterior aspect of the apex of the left ventricle, in a number of instances (3 out of 12) the main deflection was downwardly directed. Stimulation of any part of the anterior aspect of the septum consistently produced upright main deflections

in Lead S′I while stimulation of its posterior surface resulted in negative waves. It would therefore appear that the direction of the main deflection in either Lead RL (combination of electrodes on right and left borders of the heart anteriorly) or L′R (one electrode on left border posteriorly and other on right border anteriorly) will localize the site of origin of premature contractions to one or the other ventricle, while the direction of the main deflection in Lead S′I (one electrode on superior border posteriorly and other on inferior border anteriorly) limits it generally to either the anterior or posterior surface of the heart.

Effect of Change in the Position of the Heart on the Direction of the Curves Resulting from Artificial Stimulation. In order to test further the accuracy of the experimental chest leads in localization, a procedure similar to that of Katz and Ackerman [7] was carried out in the present investigation. In seven instances, the heart was pulled and rotated to the left so that its anterior surface consisted almost entirely of right ventricle, and in six, traction was applied in the opposite direction so as to cause more of the left ventricle to be situated anteriorly. Records of extrasystoles, arising from the two surfaces of the ventricles close to their lateral borders, were obtained before and after the above manipulations and these were compared as to the direction of the main deflection. In nine out of 13 trials a change was noted in Lead S′I. In nearly every instance the alteration in direction could be explained by the fact that the extent of rotation of the heart was usually sufficient to change a previously posterior position to one now anteriorly situated, and vice versa; these results therefore coincided with the differences noted in S′I as one or the other surface was stimulated with the heart in the normal position. In one case, the main deflection in RL was reversed, but in no instance was a change noted in Lead L′R, even in the face of marked rotation and traction of the heart.

In the case of the standard leads and Lead IV considerable alterations were observed following the procedure; the results in these conforming generally to those reported by Katz and Ackerman. In five out of 13 cases the main deflection of the extrasystolic wave was reversed in Lead I and in nine cases, in Lead III. The main deflection in Lead IV was altered in all seven instances in which it was recorded. One can therefore conclude that generally the main deflection in the experimental chest lead which designates the ventricle involved (Lead L′R) is less susceptible to change with alteration in the position of the heart than is the main deflection in the standard leads and Lead IV.

Relative Position of the Electrodes in the Experimental Chest Leads. As in the previous investigation, steps were taken to determine whether or not the most accurate results in localization would be obtained only if the two linear electrodes in the combination were situated on the chest and in a certain definite relationship to each other. Accordingly, various substitutions for one or the other of the two electrodes in Leads L′R (which

TABLE I

Localization of Premature Contractions by Means of the Multi-Plane Chest Leads

Site of Stimulation	Multi-Plane Chest Leads							
	L'R			S'I			RL	
	No. of Cases	Main Wave Positive	Main Wave Negative	No. of Cases	Main Wave Positive	Main Wave Negative	No. of Cases	Main Wave Positive	Main Wave Negative
Right ventricle, anterior surface	10	0	*10*	8	*8*	0	8	*8*	0
Left ventricle, anterior surface	10	*10*	0	12	*9*	3	7	0	*7*
Septum, anterior aspect	2	0	2	3	*3*	0	2	2	0
Right ventricle, posterior surface	8	0	*8*	8	0	*8*	8	*8*	0
Left ventricle, posterior surface	8	*8*	0	8	0	*8*	5	0	*5*
Septum, posterior aspect	3	0	3	4	0	*4*	3	3	0

designated the ventricle) and S′I (which designated surface of heart) were made. These modifications consisted of:

1. Substituting a large oval electrode situated on the anterior chest wall, so as to overly the heart, for the anterior linear electrodes R and I in Leads L′R and S′I respectively.
2. Substituting a similar type of electrode placed on a corresponding spot on the back for the posterior linear electrodes L′ and S′ in the same leads.
3. Combining first the posterior linear electrode and then the anterior one in each of the two experimental chest leads with an ' indifferent ' electrode on the left leg.

In the case of the various modifications of Lead L′R employed, it was found that results, which could be utilized for localization of the site of stimulation to one or the other ventricle, were obtained only when the right anterior linear electrode was combined with an ' indifferent ' one on the left leg. In all other combinations, inconstant non-specific changes were observed.

In the case of the various modifications of Lead S′I employed, only in those instances in which the anterior inferior linear electrode was combined with a large oval electrode placed on the heart posteriorly were results comparable with those of Lead S′I obtained.

Besides the above, Lead IV was also recorded in order to observe comparable results with a lead in which two relatively large oval electrodes were placed on the chest anteriorly and posteriorly, directly over the heart. Of six instances in which the right ventricle anteriorly was stimulated, in five the main deflection in this lead was upwardly directed while in the remaining one it was negative. In reference to the posterior surface of the same ventricle, in two it was up and in the other two down. In the left ventricle anteriorly, in all instances the main deflection was positive, while in the case of the posterior sites in three it was negative and in one, positive.

To summarize, the most accurate results in localization were consistently obtained when both electrodes in the combination were situated at the estimated borders of the heart. In the case of the modifications of these leads, although some appeared to be equally efficient in localizing the surface and others the ventricle, no one type of combination was of value for both. Lead IV, in which the two electrodes were placed over the heart, was likewise of little use in this respect. On the other hand, with Leads S′I and L′R, both surface and ventricle could be localized in every instance.

Changes Observed in the Experimental Chest Leads Following the Transection of One or the Other Branch of the Bundle of His. The right branch of the Bundle of His was transected in two instances and the left in three. Consistent results were obtained in all experiments. In the case of a lesion of the right branch the main deflection in Leads RL and S′I was

negative while in L′R it was positive (figure 3*A*). On transection of the left branch, exactly the reverse findings were observed. The main deflection in RL and S′I was consistently positive while this wave in L′R was negative (figure 3*B*).

The deflections in the standard leads conformed to the new classification

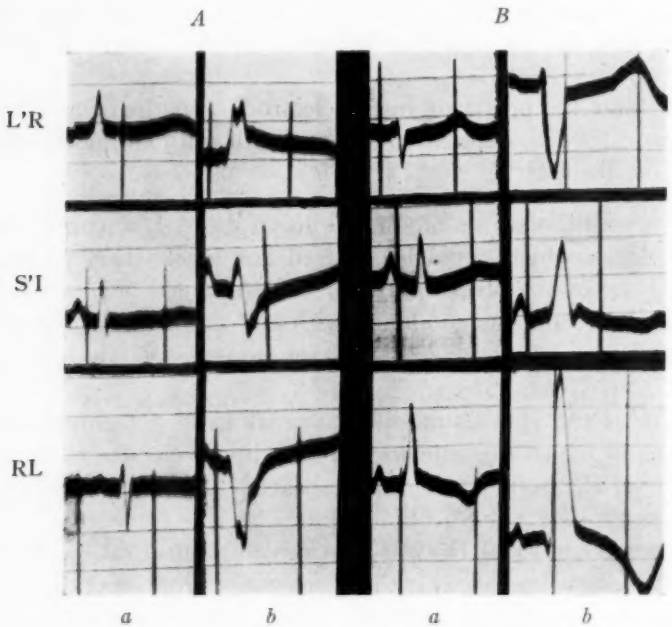

FIG. 3. Curves produced by transection of the branches of the bundle of His. *A*. Transection of right branch; *a*. Normal; *b*. After transection. *B*. Transection of left branch; *a*. Normal; *b*. After transection.

of bundle branch block [6, 8, 9] while the changes in Lead IV were not characteristic. In the latter, the main deflection in both right and left branch lesions was downwardly directed.

Comparison of the above findings with those obtained as a result of artificial stimulation of the heart reveals that activation of one ventricle before the other, either because of a bundle branch lesion or because of the origin of the impulse in one ventricle, produces similar types of alterations in the experimental chest leads.

SUMMARY AND CONCLUSION

Further evidence is presented to show that certain chest leads, employing combinations of linear electrodes placed parallel to and beyond the estimated borders of the heart, are of considerable value in (1) localizing the site of artificial impulse formation to one or the other surface of the heart as well as to one or the other ventricle, and (2) in designating the branch involved

in experimental bundle branch lesions. The tracings of premature contractions obtained with some of these leads remained unchanged even in the face of sufficient traction and rotation of the heart to produce marked alterations in the standard lead and Lead IV curves.

In view of the consistent results obtained in the present investigation, as well as in the previous one on experimental ventricular cauterizations, it seems reasonable to assume that these experimental chest leads should be of value when applied clinically in the identification and localization of comparable conditions.

REFERENCES

1. Abramson, D. I., and Weinstein, J.: Characteristic variations in combinations of linear chest electrodes (multi-plane chest leads) resulting from experimental ventricular lesions, Am. Jr. Physiol., 1935, cxi, 382–391.
2. Weinstein, J.: Multi-plane electrocardiography, Ann. Int. Med., 1934, vii, 1503–1512.
3. Wood, F. C., and Wolferth, C. C.: Experimental coronary occlusion, Arch. Int. Med., 1933, li, 771–788.
4. Wilson, F. N., Johnston, F. D., and Hill, I.: Interpretation of galvanometric curves obtained when one electrode is distant from heart and other near or in contact with ventricular surface, Am. Heart Jr., 1934, x, 176–189.
5. Hoffman, A. M., and Delong, E.: Standardization of chest leads and their value in coronary thrombosis and myocardial damage, Arch. Int. Med., 1933, li, 947–964.
6. Roberts, G. H., Crawford, J. H., Abramson, D. I., and Cardwell, J. C.: Experimental bundle-branch block in the cat, Am. Heart Jr., 1932, vii, 505–513.
7. Katz, L. N., and Ackerman, W.: The effect of the heart's position on the electrocardiographic appearance of ventricular extrasystoles, Jr. Clin. Invest., 1932, xi, 1221–1239.
8. Wilson, F. N., Macleod, A., and Barker, P. S.: The interpretation of the initial deflection of the ventricular complex of the electrocardiogram, Am. Heart Jr., 1931, vi, 637–664.
9. Wilson, F. N., Macleod, A., and Barker, P. S.: Order of ventricular excitation in human bundle-branch block, Am. Heart Jr., 1932, vii, 305–330.

THE EFFECTIVENESS OF ACETYL-B-METHYLCHOLINE GIVEN BY MOUTH AS A VASODILATING AGENT *

By GRACE A. GOLDSMITH, M.D., *Rochester, Minnesota*

CHOLINE and its compounds have been investigated extensively in recent years. Acetylcholine was first prepared by Baeyer in 1867 but remained of chemical interest only until Hunt and Taveau in 1906 noted its marked physiologic activity. Both choline and acetylcholine have been isolated from animal tissues, Dale obtaining the latter in pure chemical form in 1929. Acetylcholine owes its present importance to the almost certain proof that it is the chemical intermediary between parasympathetic nerve stimulation and tissue response (Dale and Alles).

Acetylcholine has three important actions: (1) a parasympathetic effect, inhibiting cardiac action and increasing intestinal tonus; (2) a vasodilating effect, and (3) a nicotine-like effect, causing a rise in blood pressure when its other actions have been abolished by atropine. Acetylcholine has not been useful in clinical medicine as it is rapidly destroyed on contact with blood by enzymic catalyzed hydrolysis.

Acetyl-B-methylcholine was synthesized by Major and his colleagues, and its physiologic properties were tested first by Simonart and later by Comroe and Starr. The effects produced were similar to those caused by stimulation of the parasympathetic nervous system and were accompanied by dilation of peripheral blood vessels. The drug, being less readily destroyed by the body esterases than acetylcholine, was effective when administered orally and subcutaneously.

Starr, Elsom, and Reisinger found that acetyl-B-methylcholine given subcutaneously in doses of 2.5 to 25 mg. caused a fall in blood pressure, a rise in pulse rate, flushing, and sweating. The action began within one minute and lasted from 15 to 20 minutes. Acetyl-B-methylcholine given orally caused a fall in blood pressure, a diminution in the pulse rate, and increased intestinal peristalsis. Effective dosage by mouth was from 50 to 100 times that of subcutaneous injection. The action began 15 to 75 minutes after administration and lasted from a half to one hour. Skin temperature was slightly increased in three of five cases.

Starr gave acetyl-B-methylcholine orally to four patients with Raynaud's disease, with resulting partial relief of the spasm that is excited by mild degrees of cold. One patient with thromboangiitis obliterans had a rise in skin temperature of 1.8° C. after taking 300 mg. of acetyl-B-methylcholine by mouth. The drug caused temporary reduction in blood pressure in most cases of hypertension in his series.

* Submitted for publication August 16, 1935.
From the Mayo Clinic, Rochester, Minnesota.

Kovacs and Kovacs used acetyl-B-methylcholine by iontophoresis in chronic arthritis and in a few cases of peripheral vascular disease. They obtained an increase in skin temperature in the areas treated which lasted from two to eight hours. Two patients suffering from digital ulcers in cases of Raynaud's disease exhibited rapid healing of the lesions.

Page, who administered this drug subcutaneously to hypertensive patients, found a drop in blood pressure and an increased temperature of the skin of the face and trunk, the hands and feet being almost unaffected. The electrocardiogram often showed an inverted T-wave. The heart rate was increased. Given by mouth in doses of 4 gm. the blood pressure was affected little or not at all.

The present study was undertaken to investigate further the effects of the oral administration of acetyl-B-methylcholine (mecholin) * on the temperature of the skin, pulse rate and blood pressure of subjects who had disease of the blood vessels. The drug was given to 29 patients in doses of 50 to 1500 mg. Experiments were conducted in a room of constant temperature, the subject having rested a half hour or more to allow the blood pressure, pulse rate, and skin temperature to reach a constant level. The temperature of the skin was determined by thermal junctions attached to the fingers and toes. Readings were taken at intervals of 15 minutes for a period of several hours.

Effects of Acetyl-B-Methylcholine Administered Orally

Effect on Skin Temperature. The effect of the oral administration of acetyl-B-methylcholine on the temperature of the skin in the cases studied is given in table 1. Any rise of 2° C. or less was considered insignificant. Only three patients failed to show such an increase, and of these two received small and insufficient doses. The average maximal rise was 5.82° C. and the average high temperature attained in the digits was 33.1° C.

In 13 cases there was a rise of more than 6° C. In cases in which vascular spasm rather than organic occlusion predominated; namely, in cases of hypertension and Raynaud's disease, vasodilation was greatest. Smaller doses (50 to 100 mg.) were effective in some instances in cases of Raynaud's disease, whereas in cases of arteriosclerosis and thromboangiitis obliterans from 1,000 to 1,500 mg. were needed to produce significant vasodilation. In eight cases a rise in temperature occurred in the fingers but none in the toes. Three of these patients received doses of less than 200 mg. Larger doses seem necessary to open up the vessels in the feet. Particularly in Raynaud's disease the fingers were more readily affected.

There was marked variability in the rise in cutaneous temperature in the various digits in cases of Raynaud's disease, and less variability in cases of arteriosclerosis and thromboangiitis obliterans. In one case of Raynaud's

* Acetyl-B-methylcholine (mecholin) for this investigation was furnished through the courtesy of Merck and Company.

TABLE I

Effect of Acetyl-B-Methylcholine on Skin Temperature

Diagnosis	Cases	Maximal rise in skin temperature, degrees C.	Actual skin temperature, degrees C.
Hypertension	4	Average 6.62 Range 3.1 to 9.6	34.7 33.4 to 36.0
Raynaud's disease and scleroderma	8	Average 7.45 Range 3.0 to 9.9	32.65 27.0 to 35.0
Thromboangiitis obliterans	7*	Average 3.67 Range 0.9 to 7.0	32.80 29.6 to 35.6
Arteriosclerosis	5*	Average 4.72 Range 1.0 to 7.3	32.58 27.4 to 35.9
Miscellaneous	5*	Average 6.65 Range 1.5 to 10.5	32.54 26.4 to 36.9
Total	29	Average 5.82	33.11

* In one case in each of these groups there was no appreciable rise in skin temperature (less than 2.0° C.).

disease the rise in the temperature of the fingers varied from 1.9° C. in one digit to 8.1° C. in another. In one case of arteriosclerosis there was a rise of 1.6° C. in one toe and of 7° C. in another. Organic occlusion of smaller vessels would readily explain this variation. The patients who had hypertension and those of the control group gave evidence of a uniform rise in all digits.

The action of acetyl-B-methylcholine began from 15 minutes to two and a half hours after its oral administration; in 50 per cent of the cases it took effect in from 30 minutes to an hour. The maximal rise in skin temperature usually was attained in from one to three hours. The height of vasodilation was reached in less than one hour in three cases in which small doses were given and in more than five hours in two cases in which 1500 mg. of the drug were given. The duration of the rise in cutaneous temperature varied from one to six hours. In seven cases it was more than four hours, and in six additional cases more than three hours. Many experiments were terminated before the temperature returned to the original level. By repeating a dose of 1500 mg. in three or four hours vasodilation could be maintained for seven or eight hours. The effect of the drug in a case of thromboangiitis obliterans in which the patient was given 1500 mg. at the onset of the experiment and four hours later another 1500 mg. is shown in figure 1. Seven hours after the first dose the cutaneous temperatures were still considerably elevated. Room temperature remained at 24° C. The other digits behaved similarly. Variations in blood pressure and pulse rate, as can be seen, were too small to be significant.

In three cases a comparison was made between the efficiency of acetyl-B-

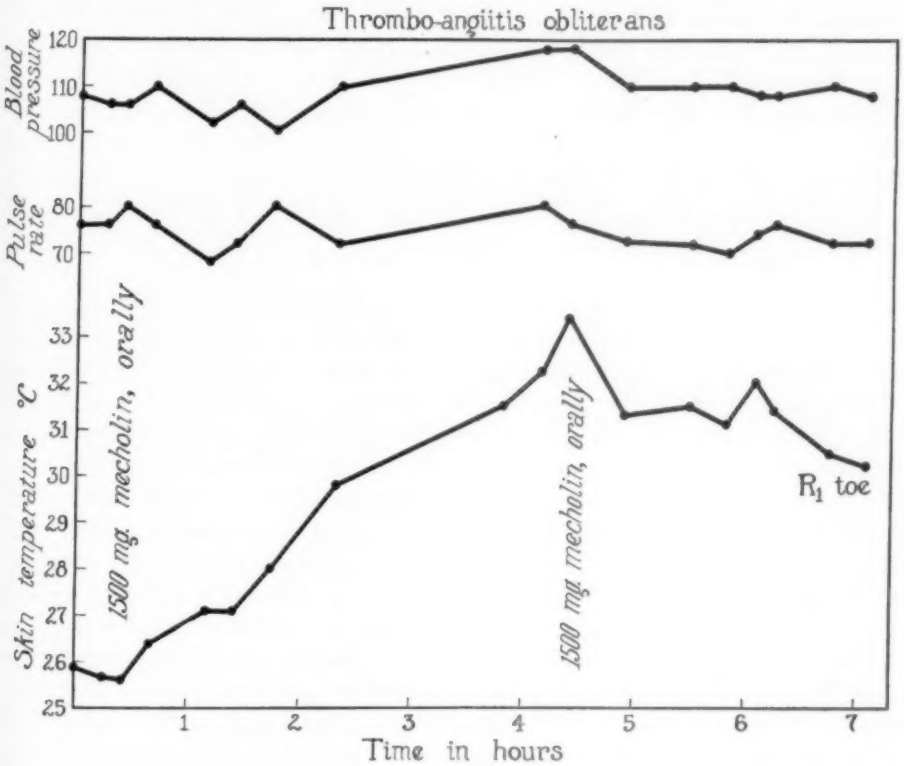

FIG. 1. The effect of repeated doses of acetyl-B-methylcholine on skin temperature.

methylcholine and typhoid vaccine as vasodilators. If the latter is assumed to be 100 per cent efficient, acetyl-B-methylcholine in these instances averaged 75 per cent in vasodilating ability.

Effect on Exposure to Cold in Raynaud's Disease. A patient with Raynaud's disease was given an ice water test to ascertain the effect of acetyl-B-methylcholine on the reaction of the blood vessels in the fingers to exposure to cold. Skin temperatures of the digits were taken until they reached a stable level. The hands were then immersed in ice water at 13.5° C. for three minutes. The color reactions were noted, and the temperatures were recorded immediately after removal of the hands from the water and at intervals thereafter. The next day, the entire test was repeated one hour and again two hours after 1 gm. of acetyl-B-methylcholine was given by mouth. Changes in color were less marked, and the temperature of the skin did not fall to quite as low a level after the drug had been administered as it had during the control test. In addition to this the hands warmed up much more quickly in the tests performed after acetyl-B-methylcholine had been given and returned to normal in less than 30 minutes, whereas in the control test it took from one to one and a half hours for all the digits to reach their original temperature levels.

Effect on Pain of Peripheral Vascular Disease. The administration of acetyl-B-methylcholine did not relieve any of the severe grades of pain in occlusive disease of the blood vessels. Patients with mild discomfort experienced a sensation of warmth and often remarked that their extremities were more comfortable after taking acetyl-B-methylcholine. One patient with ischemic neuritis due to thromboangiitis obliterans was given 7.5 gm. of acetyl-B-methylcholine in 48 hours without relief from pain. Another patient who had pain caused by an ulcer received 6 gm. in 36 hours without relief.

Effect on Intermittent Claudication. Acetyl-B-methylcholine was given in two cases in which intermittent claudication was a prominent complaint. The patients were tested by the standard exercise test before the drug was administered and at the height of the ensuing vasodilation. The pain of claudication appeared after the same amount of walking during the control and test periods.

Effect on Blood Pressure. Acetyl-B-methylcholine given by mouth had no appreciable effect on the blood pressure in this group of cases. Spontaneous variations in blood pressure, even in a resting condition, are considerable, so any change of less than 15 mm. of mercury was not considered significant. Using this standard, 16 of 27 cases showed no change in the systolic and 22 cases no change in the diastolic pressure. Seven cases showed an increase and four a decrease in the systolic pressure. Five cases showed a rise and none a fall in diastolic blood pressure. The disease from which the patient was suffering did not influence the blood pressure as to whether it rose or fell. The response of the blood pressure to the cold test (Hines and Brown) was determined in 10 cases before and at the height of the reaction to acetyl-B-methylcholine. No change was noted.

Effect on the Pulse Rate. The pulse rate was observed in 23 of 29 cases. In 14 cases there was no change. In four cases there was a rise of 10 beats or more per minute and in five cases a fall of similar degree. Three of the four patients who showed an increased pulse rate received more than 1500 mg. of the drug.

Additional Effects. In this series of cases additional effects produced by acetyl-B-methylcholine given by mouth were: (1) a sensation of warmth, localized or generalized in 50 per cent of the cases, (2) flushing of the hands or face in 25 per cent, (3) increased perspiration in 20 per cent, and (4) a mild laxative effect, in most of the cases. The only untoward symptoms were mild gas pains and nausea in two cases, one after a small dose of 50 mg. and one after 1000 mg. of the drug had been given.

Effects of Subcutaneous Administration

Acetyl-B-methylcholine was given subcutaneously to two patients who had hypertension and to one patient who had thromboangiitis obliterans. The typical effect of a dose of 20 mg. was an immediate and marked fall in

systolic and diastolic blood pressure, a rise in pulse rate, flushing of the face, sweating, and salivation. Nausea and substernal pain were noted in one case. There was a fall in the temperature of the skin of the feet which was probably a compensatory phenomenon. The action began within two minutes after injection and lasted 30 to 45 minutes.

The differences in the effects of subcutaneous and oral administration of the drug are striking. When taken by mouth, the vasodilating action predominates and there is little influence on blood pressure and pulse rate. Large doses are needed and the reaction is slow and prolonged. Subcutaneous administration affects primarily the blood pressure, causing uncomfortable side actions of sweating, salivation, and nausea, the action being rapid and evanescent.

Summary and Conclusions

Acetyl-B-methylcholine administered orally to 29 patients in doses of 50 to 1500 mg. caused an average maximal rise in the temperature of the skin of the digits of 5.82° C. Vasodilation failed to occur in only one case in which an adequate dose was given. The vasodilating effect of acetyl-B-methylcholine varies tremendously with different patients, in different pathologic conditions and in the different digits of a given individual.

The vasodilation resulting from the oral administration of acetyl-B-methylcholine is slow in onset and is of relatively long duration. An adequate dose seems to be between 1000 and 1500 mg., and this dose may be repeated every three or four hours to maintain vasodilation. No untoward results have followed the administration of 3 to 4.5 gm. in 24 hours.

No significant changes were produced in blood pressure or pulse rate in the cases studied.

Acetyl-B-methylcholine seems to be a promising drug for use in peripheral vascular disease because of its vasodilating properties, its prolonged action, its safety, and its ease of administration. The clinical use of this drug is limited at present owing to its relatively high cost.

BIBLIOGRAPHY

1. Alles, G. A.: The physiological significance of choline derivatives, Physiol. Rev., 1934, xiv, 276–304.
2. Baeyer: Quoted by Alles.
3. Comroe, J. H., Jr., and Starr, I., Jr.: Further studies on the pharmacology of acetyl-B-methylcholine and the ethyl ester of B-methylcholine, Jr. Pharmacol. and Exper. Therap., 1933, xlix, 283–299.
4. Dale, Sir H.: Chemical transmission of the effects of nerve impulses, Brit. Med. Jr., 1934, I, 835–841.
5. Hines, E. A., Jr., and Brown, G. E.: A standard test for measuring the variability of blood pressure: its significance as an index of the prehypertensive state, Ann. Int. Med., 1933, vii, 209–217.
6. Hunt and Taveau: Quoted by Dale.
7. Kovacs, R., and Kovacs, J.: Newer aspects of iontophoresis for arthritis and circulatory disturbances, Arch. Phys. Therapy, 1934, xv, 593–598.

8. MAJOR: Quoted by Alles.
9. PAGE, I. H.: Acetyl-B-methylcholine (mecholin); observations concerning its action on blood pressure, skin temperature and heart, as exhibited by electrocardiogram of hypertensive patients, Am. Jr. Med. Sci., 1935, clxxxix, 55–64.
10. SIMONART: Quoted by Alles.
11. STARR, I., JR.: Acetyl-B-methylcholine: III. Its action on paroxysmal tachycardia and peripheral vascular disease, with a discussion of its action in other conditions, Am. Jr. Med. Sci., 1933, clxxxvi, 330–345.
12. STARR, I., JR., ELSOM, K. A., and REISINGER, J. A.: Acetyl-B-methylcholine. I. The action on normal persons, Am. Jr. Med. Sci., 1933, clxxxvi, 313–323.

BLACKWATER FEVER: A CLINICAL REVIEW OF FIFTY-TWO CASES *

By M. FERNÁN-NÚÑEZ, M.D. (Madrid), *Milwaukee, Wisconsin*

THE conquest of the diseases of the tropics by modern medicine has been one of the most dramatic applications of science during the progress of civilization. The causative agent of practically every tropical disease has been discovered and an effective sanitary protection and specific treatment provided against each one.

The population pressures and economic difficulties of life in the more crowded countries of the world demand that the fertile and sparsely peopled tropical lands be made available for settlement. In the tropics there still remains one major disease, hemoglobinuric fever, which is the terror of the white man. To it an enormous amount of research has been devoted with but little addition to our knowledge of its etiology and therapy.

The objective of this paper is to emphasize a different line of investigation which offers a promise of affording insight into the mechanism of this terrible malady, and to restate briefly most of the important established facts concerning it, giving to the whole an interpretation based upon the experience of the writer in the treatment of 52 cases of hemoglobinuric fever and the observation of as many more patients of other practitioners in tropical practice.

This disease syndrome has received various designations: Hemoglobinuric Fever, Blackwater Fever, Hemorrhagic Malarial Fever, Black Jaundice, Canebrake Yellow Fever, etc. The descriptions in the literature indicate that it has often been confused with the bilious types of malaria, with yellow fever, with the icteroid manifestations of various spirochetal infestations (icterohemorrhagic fever, relapsing fever, dengue, etc.) and with toxic and symptomatic hemoglobinurias.

Early accurate clinical descriptions of it were written by physicians in New Orleans (1832), Georgia (1835), the Wabash River valley of Indiana (1837), the White River valley of Illinois (1843), and subsequently in the Great Lakes region and Canada, the Pacific coast, New Jersey, Pennsylvania, New York, Connecticut and Rhode Island.

Since its discovery in the United States and Europe it has become more frequent in the tropics due to the increased migration there of the white races, in which it is chiefly found. Its incidence and geographical distribution parallel exactly those of estivo-autumnal (malignant subtertian) malaria, of which the *Plasmodium falciparum* is the known causative agent.

* Received for publication November 23, 1935.

Etiology

With a disease so spectacular in its manifestations and mortality, and in which no specific causative agent has yet been discovered, it is quite natural that many theories should have arisen to explain it.

The Malaria Theory. The disease appears only in malarial districts and in persons who are being treated for malaria, its ratio corresponding almost exactly to the percentage of estivo-autumnal malaria in a community.

The Quinine Theory. The attacks often follow immediately on the taking of quinine, and sometimes the patient's condition improves on the stoppage of quinine.

The Allergic Theory. The present writer believes that blackwater fever is merely an allergic manifestation of malaria in which quinine, exposure and various other resistance-reducing agencies aid in precipitating the attack. It occurs chiefly in Europeans who have had one or more attacks of estivo-autumnal fever during a residence usually of at least two years in the tropics. In such an individual sensitized by previous attacks a new attack of estivo-autumnal malaria or the administration of quinine in a latent case brings on the acute syndrome by the liberation of allergens.

The author's intradermal test with suspensions of *Plasmodium falciparum* rendered non-infective (Plasmodoid) was applied in a group of persons of Caucasian extraction who had resided in an endemic area of Colombia for more than six months. Following the removal of those showing a positive sensitivity, blackwater fever disappeared from that area.

Symptoms

In typical cases the patient suffers a sudden attack which resembles a rather severe paroxysm of malaria with chill, fever, sweat, headache, and more marked exhaustion than accompanies the usual malarial attack. This is followed by hemoglobinuria. The patient is greatly depressed and very ill. The mind is clear but there is restlessness and anxiety. In favorable cases improvement is observed on the second day.

Urine. The fresh urine contains oxyhemoglobin, an increase in urobilin, an unknown pigment (hemozoin?), and a marked albuminuria. Upon standing methemoglobin quickly forms and the urine turns black (blackwater). Red cells are absent and the fresh urine is usually clear, not smoky as when unaltered blood is present. The specific gravity is around 1.025. On shaking the foam is pinkish in color. The reaction is markedly acid and acetone bodies are present. There are granular and pigmented casts. In the average case the hemoglobin in the urine is equal to that in 300 c.c. of blood, but the red cell destruction is often many times as great as the amount of blackwater would lead us to suppose, since much of the pigment is broken down or deposited in the reticulo-endothelial system throughout the body.

Often in the ambulant type the first intimation the patient has that anything is the matter is the passing of black urine. He may feel extraordinarily well and pyrexia may be absent, but the pulse rate is usually increased.[1] At times hemoglobinuria may be entirely absent, due to the breaking down of the pigments by the reticulo-endothelial system, or it may appear on and off. Specimens should be collected in separate containers at different time intervals.

Fever. The fever at the beginning is usually around 101° F. but may run up to 104° or 105° F. quickly, then subside somewhat after the sweat, but does not always return to normal, being continuous or remitting, and at times resembling the temperature curve of spirochetal relapsing fever. In atypical (ambulatory) cases the temperature may be subnormal.

Jaundice. This comes early, is intense and appears at the same time as the hemoglobinuria. Being a hemolytic jaundice it differs from the obstructive type in that there is no retention of bile salts in the blood. Itching of the skin is not marked, there is no bradycardia, no prolongation of the coagulation time and no hemorrhages due to injury of the capillary endothelium by bile salts.

Vomitus. This is "leafy green" and accompanied by epigastric distress. The feces always give the reaction for occult blood, and in severe cases blood and hemoglobin may be passed per anum, as in dysentery.[2]

The *pulse* is rapid, 110 to 150 per minute, feeble and of low tension, in severe cases resembling that of shock. It differs thus from the slow pulse of yellow fever and obstructive icterus.

Blood. Within 24 hours the erythrocytes may be reduced to 2,500,000 and later in the attack to 1,000,000 per cu. mm. The hemoglobin is correspondingly decreased, but hemoglobin estimations are very inaccurate since the plasma is deeply colored with free hemoglobin. The leukocyte count shows an increase in the phagocytic melaniferous monocytes (up to 24 per cent), which is explained by their being a part of the reticuloendothelial system. The sedimentation time is decreased, and there is reduction in the coagulation time.[3] During the first 48 hours approximately 20 per cent of cases show malarial parasites in the blood, chiefly subtertian rings, which usually rapidly disappear.

Five c.c. of blood placed on ice for 5 minutes, then incubated at 37° C. for one hour, show no hemolysis, thus differing markedly from the blood in paroxysmal hemoglobinuria ("autolytic reaction").[4]

The *spleen* is enlarged and tender. Tissue smears from the splenic pulp and rib marrow reveal parasites in 30 per cent of cases.[2]

Anuria is the most feared complication. It is practically complete, but the patient remains perfectly *compos mentis*, and with no edema for 12 to 14 days, and then dies after a few hours of increasing unconsciousness. Patients seldom recover if the suppression lasts more than 24 hours.

Antecedent abdominal disease is apt to light up. Appendicitis, intus-

seption, gastritis, cholecystitis, severe colics, relapse of amebic dysentery, obstinate constipation may occur.

Relapses are exceedingly common in cases which have moved or been moved, or are even restless in bed, in from 48 to 72 hours, and such relapses may be more than six in number, each one leaving the patient in a weaker state. Cases moved are liable to very sudden and alarming jaundice. Severe anemia and nephritis increase the tendency to relapses.[1]

Pathology

Few reports of systematic postmortem studies of hemoglobinuric fever cases are available and our knowledge of the pathognomonic pathology is rather meager. Necropsies are usually performed 8 to 10 days after the beginning of an attack and, as death is then due to anemia or urinary suppression, these examinations may show little evidences of malaria. The writer performed autopsies on 11 cases of fatal blackwater fever and the observations are here summarized.

In 20 per cent of cases of estivo-autumnal malaria one ordinarily finds in the peripheral blood only the early ring forms of schizonts and the gametocytes (crescents). The later stages of schizogony are carried out in the internal organs. The large segmenting forms are held in the capillaries by the reticulo-endothelial cells, which accounts for their tendency to agglutination with occlusion of vessels supplying important organs, and explains why the pernicious forms of malaria (comatose type, etc.) are found chiefly in malignant tertian.

During the anaphylactic attack which initiates the hemoglobinuria the parasites are destroyed along with the parasitized red cells, parasites rarely being found in great numbers during the illness or postmortem, but the pigment from the parasites remains and is deposited in the reticulo-endothelial cells of all organs of the body.

The *kidneys* are swollen and the surface is a deep red or mottled red and yellow. The cortex is widened and ecchymotic due to the hemoglobin in the tubules, and yellowish if the jaundice is severe. The pyramids are a deep purple color and sometimes show minute hemorrhages.

Microscopically the glomerular tufts show thromboses of degenerated parasites and pigment. There is cloudy swelling of the tubular epithelium which contains great quantities of hemosiderin, as shown by the Prussian-blue reaction. The tubules, especially the loops of Henle, are obstructed with hemoglobin, agglutinated erythrocytes and epithelial casts, the markedly acid urine favoring coagulation of the hemoglobin.

The *spleen* weighs 400 to 600 grams, is very friable, and presents a soft bright red or purple velvety pulp. Its capsule is smooth and thin. The malpighian corpuscles are grossly opaque and well outlined.

The splenic sinuses are distended with blood and agglutinated cells with marked phagocytosis of the red cells by the reticulo-endothelial elements.

Malarial pigment is usually abundant. The Prussian-blue reaction for hemosiderin shows focal necrosis due to infarction.

If there has been chronic malarial splenomegaly the spleen will be slaty or jet black due to the large amount of pigment, and the walls of the blood vessels will be thickened.

The *liver* is enlarged, of a pale chestnut brown color and shows focal necroses of toxic origin. The sinusoids are dilated and erythrocytes are seen agglutinated around the Kupffer cells. The hepatic cells, especially around the central vein, show increase in the albuminous granules. Small hemorrhagic areas are present in the midzonal region of the hepatic lobules. The Prussian-blue reaction for free iron is intense.

The bile is usually very thick in the gall-bladder due to the sudden and enormous destruction of red cells and some times may be turned out as a solid mass. In ordinary malaria the hemolysis is not sufficiently intense to lead to formation of pigment concretions, but in hemoglobinuric fever inspissated nodules may quickly form and cause symptoms of cholelithiasis. The gall-bladder wall shows no changes referable to the blackwater fever itself except deep pigmentation of the mucosa.

The *brain* is pale and waxy. On microscopic examination it may show edema and various capillaries filled with malarial pigment and hemoglobin. Hemorrhages and thrombi are sometimes seen. There is no staining of the brain substance by the jaundice as is notable in the other tissues of the body.

The *heart muscle* is soft and flabby and microscopically shows swelling of the muscle cells, considerable loss of striation, deeply staining nuclei, albuminous and fatty degeneration.

The *bone marrow* is usually hyperplastic as a result of the anemia, and its vessels and macrophages contain much pigment.

The mucosa of *the stomach and intestines* shows marked discoloration due to hemoglobin.

There is rather intense yellowish discoloration of all the tissues of the body, due to the presence of bile pigment in the blood plasma.

Differential Diagnosis

Paroxysmal hemoglobinuria may be impossible to differentiate from hemoglobinuric fever. It is much more common in cold climates and should always be suspected when cases of the latter disease seem to appear in non-malarial districts. There is practically always a definite history of chilling of the body immediately preceding the paroxysm. The patient is usually in much better general health and recovers from the attack much more quickly than is common in blackwater fever. It is never fatal.

Yellow Fever. On the fourth day hematuria (not hemoglobinuria) with smoky urine, and progressive jaundice begin and "black vomit" appears. Faget's sign, high temperature (104° F.) with slow pulse (60), is observed. The spleen is not enlarged.

Bilious Malaria. The urine is yellowish (bile). The jaundice is not so intense and the yellowish vomitus not so dark as in yellow fever or hemoglobinuric fever. The pulse is slower than that seen in the "shock" (anaphylactic?) of blackwater fever. There is usually marked splenomegaly (up to 1000 grams).

Prognosis

An individual healthy in other respects usually recovers, provided he is correctly treated and *submits to it.* With urinary suppression the prognosis is extremely bad. Persistent vomiting, hiccough and relapses are ominous. The general mortality is 20 to 30 per cent.

Treatment

Blackwater fever must be thoroughly and carefully treated from the very beginning and to the end of the illness. Good treatment, including good nursing, saves lives in this disease. Early apparent improvement should not lead to slackening of treatment—relapses are common and dangerous! When the patient has recovered he should change his residence to a healthful climate as he will be prone to subsequent attacks which might cost him his life.

After experience with all the accepted methods of treatment the routine here given was adopted.

Nursing. The patient should be put to bed and *not moved* lest his hemoglobinuria increase, or, if already stopped, recur. Absolute rest in bed with good nursing is essential. Avoid chilling, eliminate unnecessary noise, keep visitors away, and use every possible means to keep the patient quiet. From the first moment push fluids and nourishment (barley water, albumin water, broths, fruit juices, glucose, etc.). Do not allow a return to normal diet until convalescence is well advanced, as hemoglobinuria may reappear.

The weakened heart muscle requires that the patient be kept in absolute relaxation for three to six weeks after the acute attack. Then he may be allowed up very slowly. At the end of the second week permit an additional pillow a day until the patient is sitting up, and very gradually allow him out of bed. Lack of care in this matter will often bring on a relapse and may cost the life of the patient.

Arsphenamines. The writer found the use of the arsphenamines so superior to quinine that he practically abandoned the latter in this disease. Neoarsphenamine ("914"), 0.2 gram in 2 c.c. of sterile distilled water, by vein often gave spectacular relief if used early in the disease. Thereafter weekly injections of 0.2 to 0.4 gram proved of great aid in combating the severe anemia and strengthening the patient during convalescence. Neoarsphenamine is possibly contraindicated in patients showing signs of toxic necrosis of the liver.

A freshly prepared solution of 5 grains (0.325) of sodium thiosulphate (hyposulphite) in 5 c.c. of sterile distilled water should be injected intravenously (through the same needle used for the "914" while in place). This will prevent any untoward effects of the neoarsphenamine without impairing its therapeutic efficiency.

Sodium thiosulphate apparently has a very specific effect on the hemoglobinuria, often stopping it within a few hours. If preferred, the drug may be given by mouth in 10 to 30 grain (0.6 to 2.0 grams) doses daily.

Acidosis. As many of the features of the attack suggest acidosis, and a condition of acidosis seems to favor hemolysis, it has been the author's custom to use intensive alkali therapy routinely. Sodium bicarbonate, 300 to 500 c.c. of a 2 per cent solution, is given intravenously daily. As the bicarbonate changes to the carbonate on prolonged heating it is best to sterilize the solution at 7 pounds pressure in a live-steam autoclave. If this is not convenient the water should be boiled, allowed to cool down to near the desired temperature for injection, and the bicarbonate added. A dilute (0.5 of 1 per cent) bicarbonate solution may be given also by the Murphy drip.

Glucose, 300 c.c. of a 5 per cent solution, daily by vein, and additional quantities by the Murphy drip are useful in combatting the acidosis and general toxemia and in nourishing the patient.

Anuria. The sodium bicarbonate and glucose solutions administered as above will aid in increasing the flow of urine and by thus eliminating the products of hemolysis from the blood shorten the period of hemoglobinuria. Early injections, before the anuria appears, may prevent the suppression. High enemas, as hot as can be borne, with a return flow tube, are often of great aid in starting the urinary flow since they bring heat directly to the splanchnic area. For the pain resulting from renal congestion hot fomentations applied to the loins are often very efficacious.

Vomiting. Alkaline waters (0.5 of 1 per cent solution of sodium bicarbonate) may be freely used. Carbonated beverages (ordinary "soda-pop") are often better tolerated by the patient than anything else, and the sugars they contain are nourishing. Iced lemonade is usually well borne. Morphine and atropine may be required.

The rapid dehydration caused by vomiting may need to be combated by saline transfusions (intravenous drip is especially useful), or 300 c.c. may be introduced high into the bowel through a rectal tube every four hours.

Magnesium citrate or other mild saline laxatives daily are usually tolerated and are very necessary for cleansing the intestines of the bile and toxins. During convalescence calomel in fairly large doses (5 grains), followed by a saline laxative, is especially indicated in clearing up the jaundice.

Stimulants. All forms of alcohol should be avoided.

Caffeine sodiobenzoate, 3 grains (0.2) twice daily, intramuscularly, stimulates the weakened heart and promotes diuresis. Adrenalin, 8 minims, (0.5 c.c.) of a 1/1000 solution, is administered intramuscularly at once and

every three hours until a total of four doses is given. This may be repeated on the second day of the disease if hemoglobinuria persists. Aside from its aid in relieving hypotension, it has a specific effect in relieving the anaphylactoid symptoms. Ephedrine in equivalent dosage, subcutaneously or orally, can be tried instead of adrenalin.

Quinine. If neoarsphenamine is not available quinine administered as here outlined may be substituted. The hemolysis of the attack causes autodestruction of the malaria parasites in 70 per cent of cases. Quinine should only be administered in those 30 per cent of cases still showing parasites in the peripheral blood. Five grains are given the first day by mouth or intramuscularly, 10 grains (0.65 gm.) the second day, 15 grains (1.0) the third day and thereafter. After convalescence, if malarial parasites are still present in the peripheral blood, quinine may be cautiously given, watching for a return of the hemoglobinuria.

Quinine idiosyncrasy should always be tested for. Inject 1 grain (0.065 gm.) of quinine dihydrochloride or bisulphate. If there is no reaction in an hour, inject 4 grains (0.25). If there is quinine hypersensitiveness this will almost surely produce a reaction. If the reaction is slight, the injection is repeated in 12 hours; otherwise it is postponed for 24 hours. The injections are continued daily until the malaria is cured. To avoid abscesses the injections should be given intramuscularly in a dilution of 1 grain in 1 c.c. of sterile water, and the skin at the site of injection thoroughly sterilized.

It is extremely doubtful whether plasmochin (plasmoquin) should ever be used in blackwater fever, except possibly in cases where there is a quinine idiosyncrasy. This drug is highly toxic, affecting especially the liver, and often causes cyanosis and hemoglobinuria in itself. Its action on the subtertian parasites is not nearly as effective as it is on the tertian. If employed at all, not over 0.03 gram, twice daily, intramuscularly, should be administered to hold the infection under control until the acute stage of hemolysis has subsided and quinine can be more safely given.

Atebrin, orally in 0.3 gram doses daily, for three doses, may be tried instead of plasmochin. As it colors the urine and skin yellow it may appear to make the disease worse.

Other Drugs. Our somewhat limited experience with the following measures did not convince us of their general utility: For anuria—tincture of cantharides (Trout), bichloride of mercury (Hearsey), cyanide of mercury, novasural and salyrgan. For hemoglobinuria—calcium lactate (Castellani), hemostatic serum (Aguilar), *Streptococcus hemolyticus* antiserum (Crawford), Bothropic antivenin (Makel) and cholesterin.

Blood transfusions in six cases left us uncertain as to their value. If used at all we would urge a careful direct matching of the bloods of the recipient and donor and repeated transfusions of small amounts (100 c.c.).

Conclusions

1. Blackwater fever is practically the one remaining tropical disease whose etiology has not been definitely solved.

2. The theory is submitted that it is an allergic manifestation of estivo-autumnal (malignant subtertian) malaria.

3. Reference is made to the author's intradermal test for the detection of individuals allergic to estivo-autumnal malaria, who if attacked again by the disease would be potential victims of hemoglobinuric fever.

4. The symptoms, pathology and treatment of blackwater fever are reviewed on the background of the writer's experience in the personal management of 52 cases of the disease and the observation of an equal number of patients of other physicians.

BIBLIOGRAPHY

1. Carmody, E. P.: Blackwater fever, Jr. Med. Assoc. of South Africa, 1929, iii, 389–390.
2. Makel, H. P., and Gilder, W.: Blackwater fever, The Military Surgeon, 1930, 156–164.
3. Menk, W.: Blackwater fever in the Banes Hospital (Cuba), Annual Report United Fruit Co. Med. Dept., 1927, 113–117.
4. Stitt, E. R.: Diagnostics and treatment of tropical diseases, 5th Ed., P. Blakiston's Sons & Co., Philadelphia.
5. Todd, J. C., and Sanford, A. H.: Clinical diagnosis by laboratory methods, 7th Ed., 319–321, W. B. Saunders & Co., Philadelphia.
6. Facio, A. A., and Rojas, M. D.: The treatment of hemoglobinuric fever with caffeine sodio-benzoate, Jr. Trop. Med. and Hyg., Liverpool, (March 18) 1925.
7. Whitmore, E. H.: Blackwater fever, Ann. Int. Med., 1928, 316–324.
8. Brahmachari, P., et al.: Studies in blackwater fever, Jr. Trop. Med. and Hyg., 1932, 309–310.
9. Ghiron, M.: On blackwater fever, Jr. Trop. Med. and Hyg., 1932, 65–71.
10. Stephens, J. W. W.: Ann. Trop. Med. and Parasit., Liverpool, 1929, 451–479.
11. Stephens, J. W. W.: Proc. Internat. Conf. on Blackwater Fever, Boston, 1925, i, 121–128.
12. Blacklock, B.: Etiology of blackwater fever, Pub. Sir Alfred Lewis Jones Research Lab., Freetown, (Feb. 5) 1923.
13. Blacklock, D. B., and MacDonald, G.: Mechanism of blackwater fever and certain allied conditions, British Med. Jr., 1928, 145–149.
14. Low, G. C.: Blood transfusion in blackwater fever, Lancet, 1928, 645–647.
15. Whitmore, E. R., and Roe, J. H.: Further study of the blood in blackwater fever, Annual Report United Fruit Co. Med. Dept., 1929, 59–64.
16. Bodechtel, G.: Ein Beitrag zur Frage de Übertragbarkeit der menschlichen Malaria auf Versuchstiere, Klin. Wchnschr., 1930, 2020.
17. Alessandro, A.: L'adrenalina nella cura della splenomegalia malarica cronica, Riv. Sanitaria Siciliana, 1932, 332, 335–338, 341–342.
18. Garnham, P. C. C.: Observations on *Plasmodium falciparum* with special reference to the production of crescents, Kenya and East African Med. Jr., 1931, viii, 2–21.
19. Chesterman, C. C.: Treatment of blackwater fever by oral sodium bicarbonate, Lancet, 1929, 1355–1356.
20. Tolleson, H. M.: Treatment of hemoglobinuric fever, Jr. Ga. Med. Assoc., 1930, xix, 53–57.
21. Del Valle, C. M.: A case of blackwater fever and its urologic aspect, N. Y. State Jr. Med., 1930, xxx, 1287–1288.

22. FAIRLEY, K. D.: Cholelithiasis as a sequel of blackwater fever, Lancet, 1930, 1395–1396.
23. MILANI, C., and CUBONI, E.: Inoculation de la malaria chez l'homme et immunite antimalarique, Boll. Sezione Ital., Internaz. di Microbiologia, Milan, III (Sept.) 1931.
24. PATERSON, J. C.: The value of plasmochin in the treatment of malaria infections encountered in some cases of blackwater fever and quinine hemoglobinuria, Am. Jr. Trop. Med., 1932, xii, 363–368.
25. WAKEMAN, A. M., MORREL, C. A., EISENMAN, A. J., SPRUNT, D. L., and PETERS, J. P.: The metabolism and treatment of blackwater fever, Am. Jr. Trop. Med., 1932, xii, 407–440.
26. Note—L'idiosincrasia chininica e la sua cura, Riforma Med., 1932, xlviii, 1115–1116.
27. BRAHMACHARI, U., BRACHMACHARI, P., and BANERJEA, R.: Studies in blackwater fever, Am. Jr. Trop. Med., 1932, xii, 117–122.
28. MANWELL, R.: Quinine and plasmochin therapy in *Plasmodium rouxi* infections and on other avian malarias, Am. Jr. Trop. Med., 1932, xii, 123–146.
29. PATERSON, J. C.: Note on the use of alkali therapy in the treatment of blackwater fever, Trans. Roy. Soc. Trop. Med. and Hyg., 1933, xxvi, 6.

THE TREATMENT OF NARCOLEPSY WITH BENZEDRINE SULPHATE *

By Helmuth Ulrich, M.D., F.A.C.P., Carl E. Trapp, M.D., and Ben Vidgoff, M.D., *Boston, Massachusetts*

Inhalation of benzedrine (synthetic racemic benzyl-methyl carbinamine: $C_6H_5CH_2CHNH_2CH_3$ [1]) for the relief of nasal congestion was found by one of us to be followed by sleeplessness, an experience that suggested the use of this method in the treatment of narcolepsy. Clinical trial showed, however, that inhalation of the drug produced very slight results, whereas oral medication was uniformly successful in preventing narcoleptic seizures. Six cases of narcolepsy have been treated by us and form the basis of this report. Prinzmetal and Bloomberg,[2] also, in a recent report published since the inception of our study, found oral treatment with benzedrine to give complete relief in nearly all of their cases.

Narcolepsy is a disease characterized by recurring attacks of diurnal sleep.† In many cases there occur also periods of muscular atony or helplessness (cataplexy). The fundamental nature of the disease is not understood. It is possible that the underlying defect is often congenital and that infections and other exciting causes (trauma, etc.) act as precipitants.[3] There is no convincing evidence, however, that the disease is hereditary or familial. It is believed by some to be the result of disturbance in the region of the basal ganglia (thalamus,[4, 5] floor of third ventricle [3]), although other portions of the brain also have been incriminated. In several reported cases of narcolepsy, the onset followed acute infectious disease, especially influenza and encephalitis.[3] Trauma [6] and over-exertion [7] also have been held responsible in a few instances. Attempts have been made to incriminate the endocrine glands, chiefly the pituitary,[8] because a tendency to obesity has frequently been observed to develop simultaneously with the onset of narcolepsy and also because in many cases the somnolence had its initial appearance in the years of adolescence.[5] A few cases have developed at the menopause. No age is exempt, although in the majority of the reported cases the onset of the disease occurred before the age of twenty-five.

The fact that six cases were admitted to the Evans Memorial within a period of one year indicates that the disease occurs with increasing frequency. It is chronic and usually incurable,[9] although spontaneous amelioration has been noted in several untreated cases, and the condition does not preclude a long and otherwise healthy life.[3] Symptoms and signs other than diurnal somnolence and loss of muscular tone include disturbed nocturnal sleep (insomnia, unpleasant and often terrifying dreams), irri-

* Received for publication January 8, 1936.

From the Evans Memorial of the Massachusetts Memorial Hospitals, Boston, Mass.

† For a detailed discussion and comprehensive bibliography of narcolepsy the reader is referred to Daniels' excellent thesis.[3]

tability, nervousness, obesity, dermographia, diminished libido, and a low basal metabolic rate. The disturbance of nocturnal sleep appears to be the most common. The other symptoms are said to occur with varying degrees of frequency.

Several forms of treatment have been recommended, including psychotherapy, endocrine medication (thyroid, pituitary), caffeine, and especially ephedrine sulphate, which was used first by Janota.[11] None of these, with the exception of ephedrine sulphate, has been notably successful.

Benzedrine is closely related to ephedrine but, according to Alles [12] has a more marked effect as a stimulant of the central nervous system. In the series of six cases reported herewith, consistently good results were obtained with the oral use of benzedrine sulphate.*

Case 1. Mrs. M. F., an American housewife, aged 52, entered the hospital on March 4, 1935, with the chief complaint of falling asleep during any monotonous procedure such as riding in an automobile, listening to a sermon, etc. The onset was three years ago. The attacks of sleep were more frequent after meals, shortly after getting up in the morning, and in extremes of heat or cold (very cold winter days or a very warm room). The duration of an attack was a few seconds to several minutes. On one occasion, she fell asleep while mixing dough and continued the operation throughout the narcoleptic attack. At times she took part in a conversation during an attack. A slight stimulus was sufficient to awake her. Prodromal symptoms consisted of diplopia and a dull feeling in the eyes.

In addition to the narcoleptic seizures, she had attacks of loss of muscular tone that were usually brought on by excitement or hearty laughter. If she was standing, she fell to the ground unless a support was at hand to lean against. During these cataplectic attacks she was fully conscious, but could not move. They lasted a few minutes and were not followed by any unpleasant sensations. Nocturnal sleep was poor and often disturbed by unpleasant dreams.

The family history was not remarkable. The previous personal history revealed that she had measles and pertussis in childhood, chicken-pox at age 21, and mumps at age 25. A year ago, a diagnosis of gastric ulcer had been made because she complained of gas and distress after meals. The menstrual history was normal. The last period occurred six months ago. She was nervous and irritable and tired easily.

There was moderate generalized obesity, the present and highest weight being 169 pounds. She had always been slightly obese, but a marked increase of weight began with the onset of narcolepsy. The teeth were in poor condition. Examination of the ocular fundi revealed moderate vascular sclerosis and an enlarged left blind spot. Pelvic examination disclosed hypertrophy, bilateral laceration and inflammation of the cervix of the uterus. Otherwise physical examination was essentially negative. The systolic blood pressure was 132 mm. mercury, the diastolic 64 mm.

The urine contained a slightest possible trace of albumin and was otherwise normal. The blood count revealed slight anemia (hemoglobin 78 per cent, erythrocytes 3,970,000), but was otherwise normal. The non-protein nitrogen was 31 mg., uric acid 3 mg., sugar 100 mg., calcium 11.5 mg., and phosphorus 2.4 mg. in 100 c.c. of blood. The Wassermann and Kahn tests were negative. The basal metabolic rate was minus 24 per cent. Cerebrospinal fluid: The fluid was slightly tinged with blood; cells, other than blood discs, numbered 21 per cu. mm., the sugar was 67 mg. per cent, the Wassermann test was negative. Roentgen-ray examinations of the skull were

* The benzedrine sulphate used in this study was supplied by Smith, Kline and French Laboratories of Philadelphia.

normal; the sella turcica measured 8 by 11 mm. and was regular in outline; the heart and lungs were normal.

Treatment with ephedrine was tried, but brought only very slight improvement. Oral benzedrine sulphate medication, 10 mg. three times daily, was begun after she left the hospital. At the end of two weeks' treatment she reported that "the first week I felt more like myself than I had for months. My whole system seemed to be alive. My head cleared and I did not have any of these peculiar spells (losing control of arms, legs, etc.). At the end of two weeks I stopped taking the tablets, and in a day or so the drowsiness returned and a slight tendency toward the peculiar spells [cataplexy]. I began taking the tablets again and that condition improved."

The treatment was omitted a second time. Two weeks later she wrote "my old spells are back upon me and seem to be just as bad. My hands are almost purple. My feet feel as if they were on ice, and across my forehead cold waves come and go and I just collapse, but pick myself right up and am all right until I have another. They certainly are very disagreeable, but not so very painful, unless I hit my head against a radiator as I have just done this evening."

She reported also that during the first period of medication the gastrointestinal symptoms recorded in the history (heartburn, gas and distress after meals) were present in an aggravated form, although she was not sure that the treatment was responsible for it. Later there was no evidence of gastrointestinal irritation by the drug. Since taking benzedrine she has slept much better and is no longer troubled unduly by unpleasant dreams.

Case 2. C. E. B., an American boy, aged 17, was admitted with the chief complaint of a constant tendency to fall asleep. This trouble began about seven years ago, was very pronounced during the subsequent three years, and then gradually subsided a little to reach its present level. There was no history of an immediately preceding illness.

He would fall asleep at any time, but especially while performing monotonous tasks (writing). Recently the attacks have lasted only a few minutes, but at first the duration was usually longer. Drowsiness has been more pronounced during warm weather and in a warm room. Occasionally he has had an attack while walking, and has lost his way. There have been no prodromal symptoms. He was easily aroused, but was made irritable thereby. There were also infrequent attacks of loss of muscular tone during which he did not lose consciousness but felt "as if my muscles won't hold me up." Such attacks have been usually elicited by excitement or laughter. They are much less frequent than they were formerly.

The family history was not relevant. The previous personal history revealed that he had mumps and pertussis before he was six years old. He was obese as a child. At age 10, at the onset of the present illness, he suddenly began to grow tall and is not obese at the present time. The present and highest weight is 155 pounds. There was slight tenderness in the right lower abdominal quadrant. The post-auricular lymph-nodes were palpable. The heart, lungs and ocular fundi were normal. The systolic blood pressure was 120 mm. mercury, the diastolic was 60 mm.

The urine and blood count were normal. The non-protein nitrogen of the blood was 34 mg., uric acid 3.8 mg., sugar 87 mg., calcium 10.5 mg., phosphorus 4.1 mg., and cholesterol (whole blood) 130 mg. per 100 c.c. The blood phosphatase was 11.2 units. The Wassermann and Kahn tests were negative. Dextrose tolerance test: Blood sugar, fasting, 92 mg.; one-half hour after dextrose, 111 mg.; one hour, 105 mg.; one and one-half hours, 105 mg.; two hours, 93 mg. Cerebrospinal fluid: Cells numbered 2 per cu. mm., the sugar was normal, globulin not increased, and colloidal gold and Wassermann tests were negative. The basal metabolic rate was minus 24 per cent. Roentgen-ray examination of the skull showed marked hyperostosis of the vault and retarded development of the sinuses; the sella turcica measured 6 by 9 mm. and was regular in outline.

Treatment with ephedrine sulphate was tried without benefit. Benzedrine sulphate, 10 mg. three times a day, was then given for two weeks with complete relief. The attacks of sleep recurred when the treatment was stopped. Resumption of the treatment was again followed by complete relief. The patient complained of slight anorexia for a few days at the beginning of each period of treatment. Ten mg. twice a day were tried. This smaller amount of medication, taken over a period of several weeks, has been practically as efficient as the larger amount. Only an occasional slight drowsiness has been present after severe physical exertion, but he has not fallen asleep.

Case 3. A. H., an American girl, aged 16, was admitted in September 1934, with the chief complaint of frequently falling asleep. In 1928, she had a febrile illness with pain in the jaw that was believed to have been mumps, although the diagnosis was not definitely established. Recovery was prompt. The tonsils were removed under ether anesthesia about a month later. About a week after that (at age 10), she fell asleep in school. Since then she has had frequent attacks of somnolence, sometimes five or six a day. They have lasted 10 to 20 minutes and usually have occurred in school, in church, in the theater, or during meals, rarely while she was walking. They were most frequent in the forenoon. An hour's sleep after the noon meal had a tendency to prevent attacks in the afternoon. Hearty laughter and, less often, anger or fear produced great weakness and a feeling of utter helplessness, as a result of which her head fell forward on the chest, and she was unable to raise or turn it. These cataplectic spells lasted five to 20 minutes. A nudge from a bystander quickly terminated them. She has had "horrible" dreams about snakes, beasts, etc., but they have been less troublesome at present. She has gradually gained weight since the onset of the present illness and now weighs 156 pounds.

Menarche occurred at age 11, one year after the onset of the narcolepsy. The periods have been normal. Thyroid medication, pushed to the point of making her nervous, has been used without benefit.

The family history was not contributory. There were no siblings. In addition to the questionable attack of mumps, she had measles at age five and chicken-pox at age eight.

Physical examination revealed moderate generalized obesity, slight hypertrichosis of the face, chest, abdomen and legs, and an oily skin. The labia minora were markedly hypertrophied. Otherwise the pelvic organs were normal. The ocular fundi, heart, lungs and abdomen were normal. The reflexes were hyperactive. The systolic blood pressure was 110 mm. mercury, the diastolic 85 mm. The pulse rate was 72 per minute.

The urine contained a very slight trace to a trace of albumin, one to four blood discs per high power field, and increased indican, but was otherwise normal. The blood count was normal. The basal metabolic rate was minus 16 per cent and minus 22 per cent in two tests. Roentgen-ray examinations: Intravenous Graham test was negative, the skull was normal, the sella turcica measured 6 by 11 mm. and was regular in outline, the heart and lungs were normal. The audiogram was normal. An electrocardiogram showed simple tachycardia (108), but was otherwise normal.

A diagnosis of narcolepsy and cataplexy, possibly on an encephalitic basis (mumps ?), was made. Treatment with ephedrine sulphate was followed by moderate improvement. She was discharged with instructions to continue the treatment.

She reëntered the hospital in April 1935 and reported that the medicine helped her for a few weeks after she left the hospital, but after the supply given her at the hospital was exhausted, she stopped taking it. Her physician then prescribed ovarian pills, apparently without effect. The attacks of somnolence were as frequent as before, and the cataplectic spells occurred about once a month and, as before, were induced by hearty laughter. She had no other complaints.

Physical examination revealed no changes since the previous entry. The urine was now free from albumin and blood. The basal metabolic rate was still low (minus 26 per cent). A dextrose tolerance test showed a fasting blood sugar of 81 mg. per 100 c.c., rising to 112 mg. one hour after ingestion of dextrose and receding to 101 mg. in two hours, to 99 mg. in three hours, and to 94 mg. in four hours. Blood calcium was 10.7 mg., phosphorus 3.7 mg., phosphatase 9.7 units. She was discharged with instructions to resume treatment with ephedrine.

The third hospital entry was in September 1935. She had stopped taking ephedrine two and one-half months before because it was no longer effective. She had reverted to her previous state with the attacks as frequent as before. There was no change in the physical examination. Inhalation of benzedrine sulphate was begun. On the following day she had only one attack of somnolence and the day after that none at all. On the third day the drug was given orally in tablet form, 10 mg. three times a day, and, although there were no attacks on that and the following day, she believed that inhalation was superior to the tablets. She was discharged with instructions to continue treatment by inhalation. About a month later she was advised to try the tablets again and to report after two weeks of treatment. She took 10 mg. three times a day and in a letter wrote that "they were much more effective than the inhaler. I did not fall asleep once all day while I was taking the pills." She was then advised to omit the treatment to note whether the complaint would return. The following report was received: The attacks "started again two days after I stopped taking [the tablets]. Upon resuming the treatment I was able to stay awake from 6:30 in the morning until 10 or 11 o'clock at night."

Case 4. R. R., an American bank clerk, aged 32, entered the hospital complaining of falling asleep in the daytime. The illness had begun insidiously about 15 years ago. At first, he could control the attacks by force of will, but the degree of somnolence had increased gradually until recently he could not control it at all. It was especially troublesome during any monotonous action, such as signing checks or riding in a train. He slept poorly at night, and had frequent unpleasant dreams. An attack lasted only a few seconds. Whatever he was doing (talking, riding or driving an automobile) he often carried on automatically during an attack. He had had two narrow escapes from accidents while driving an automobile. The tendency to sleep was worse after meals and in the middle of the afternoon. The sleep was not deep and sometimes merely a sort of semi-consciousness. He responded when spoken to and was easily aroused. There were no prodromal symptoms or after effects except anger at having been unable to prevent an attack. Hearty laughter and violent anger have produced slight cataplectic symptoms consisting of fluttering of the eyelids and a momentary weakness of the legs followed by twitching. They have been much less frequent during recent years. Nocturnal sleep was poor and often disturbed by vivid and sometimes unpleasant dreams. A year before, he had had thyroid and pituitary medication without benefit.

The family history revealed that his father had hay fever. Both parents had died of kidney trouble at age 50. There were no siblings. He was married and had four living and well children. There had been one miscarriage. During the last three years his sexual life had been unsatisfactory, apparently because his wife objected to other pregnancies. He had had measles, mumps, chicken-pox, whooping cough and scarlet fever as a child and malaria 20 to 25 years ago. The highest weight, that on admission, was 140 pounds.

Physical examination revealed abdominal obesity. The heart and lungs were normal. The systolic blood pressure was 130 mm. mercury, the diastolic 78 mm. The pulse rate was 88 per minute. He wore glasses for astigmatism. The pupils were not round. The fundi were normal. He was observed during a narcoleptic attack which he induced by reading. The sleep appeared normal; he snored heavily. Respirations were 15 per minute. The eyeballs were not rolled upward, but had a

tendency to wander. The pupils were very small. Attempts to elicit the reflexes aroused him. He answered a few questions in a normal manner and then again fell into a deep sleep.

The urine contained a very slight trace of albumin, but was otherwise normal. The blood count was normal. The non-protein nitrogen of the blood was 28 mg., uric acid 3.7 mg., sugar 96 mg., calcium 10.7 mg., phosphorus 2.9 mg., and cholesterol 190 mg. in 100 c.c. The Wassermann and Kahn tests were negative. The basal metabolic rate was minus 14 per cent; the galactose tolerance was slightly diminished. Roentgen-ray examinations: The skull plates showed expansion of the diploë with hyperpneumatization of the sinuses and beginning sclerosis of the vault. There was calcification of the pineal gland. The sella turcica measured 7 by 12 mm., and was regular in outline. Dextrose tolerance test: Fasting 100 mg.; one-half hour after dextrose, 191 mg.; one hour, 200 mg.; two hours, 193 mg.; three hours, 129 mg.; four hours, 75 mg.; five hours, 71 mg.; six hours, 90 mg.

He was discharged with instructions to use benzedrine by inhalation. He reported later that the treatment produced no appreciable effect. Oral treatment, 10 mg. three times a day, was then begun. The attacks were completely controlled. At present, after several weeks of continuous medication, he is free from symptoms, except some drowsiness while riding on a train. He sleeps well at night and is not troubled by unusual dreams. At first, he had had an occasional slight feeling of nausea when he took the tablets without water, but that is no longer troublesome.

Case 5. P. S., a colored girl, aged 12½ years, complained of frequent attacks of sleeping. There was a history of a fall at age four which her mother believed to have been responsible for the illness, although there had been no immediate ill effect. She had not been unconscious. The diurnal naps became particularly noticeable when she entered school. The teacher reported that the child went to sleep during class hours. Her mother stated, however, that she had taken long daily naps before that. The tendency to somnolence was more pronounced on hot days, but there was no predilection for a special time of the day. It occurred only when she was quiet or performing a monotonous task (knitting) and never while she was at play or when something was holding her interest. The duration of the attacks was usually an hour or two. She was easily aroused but went to sleep again if permitted to do so. She did not continue to perform previously begun actions during an attack. Cataplectic symptoms had not been noted, but at times she twitched while asleep. Treatment with thyroid, prescribed elsewhere, had been without benefit.

The family history was not relevant. Birth and infancy had been normal. She had had measles, mumps, chicken-pox, pertussis and scarlet fever. Frontal headaches were frequent, especially in hot weather. Occasionally there was tinnitus in the right ear. Her feet swelled and were cold during cold weather. Constipation was controlled by the regular use of mineral oil. Menstruation had begun six months before and had been normal except for dysmenorrhea on the first day. She tired easily, was slightly nervous and very irritable. She slept well and was not troubled abnormally with dreams. The highest weight, that on admission, was 95 pounds. Physical examination revealed nothing abnormal except flat and pronated feet which an orthopedic consultant believed to be congenital.

The urine was normal. Blood: The hemoglobin was 12 to 14 grams per 100 c.c. (74 to 78 per cent); erythrocytes numbered 3,570,000 to 3,970,000 per cu. mm.; leukocytes 8,500 to 9,700, of which 12 to 21 per cent were eosinophiles. The non-protein nitrogen was 26 mg.; uric acid 2.8 mg.; sugar 80 mg. and cholesterol 202 mg. in 100 c.c. blood. Feces: No ova or parasites were found. Dextrose tolerance test: The fasting blood sugar was 83 mg.; one hour after dextrose it was 141 mg.; in two hours it was 121 mg.; in three hours, 115 mg.; in four hours, 112 mg.; in five hours, 83 mg.; and in six hours, 93 mg. The basal metabolic rate was minus 23 per cent. The galactose tolerance was moderately diminished. Roentgen-ray examinations:

The skull was normal, the sella measured 6 by 12 mm. and was regular in outline. The sinuses were normal. Cerebrospinal fluid: Manometric readings were normal; cells numbered 1 per cu. mm.; the sugar content was normal; globulin not increased; the colloidal gold and Wassermann tests were negative.

Benzedrine sulphate, 10 mg. three times a day, was prescribed. It gave marked relief, but some degree of somnolence still occurred at the end of the morning and toward evening. The amounts of the drug taken in the morning and at noon were then increased to 20 mg. each, the evening dose remaining at 10 mg. Since then she has been free from attacks throughout the day, except slight drowsiness in late afternoon. Her mother reports that she appears normal in every way but that the increased medication induced an additional menstrual period (3 periods in 1 month). An occasional feeling of fullness at meals, not noticed before, has been present during the past two weeks.

Case 6. W. L., a Nova Scotian farmer, aged 22, complained of "falling asleep in the middle of the day's work." The illness began about six years ago with what he described as "a breakdown in health," consisting of nocturnal insomnia, nervousness, excitability and increased drowsiness in school. He stated that before that time he was well, but more searching questioning elicited the information that he had had mild attacks of sleepiness in school during the preceding year or two.

Recently the attacks of diurnal sleep, about four or five a day, have lasted from a few seconds to several minutes. They have occurred at any time of the day. He has been easily aroused but has been irritated thereby. If he awoke spontaneously, he felt refreshed. A warm room, monotonous procedure and inactivity favored the onset of an attack. Automatic action was frequent. He slept poorly and had unpleasant dreams about being pursued by animals. Excitement, anger, or hearty laughter often caused his muscles to relax; "they would not do what I wanted them to do." During these cataplectic spells he was unable to speak but remained conscious. Their duration was but a few seconds. He believed that they were less frequent than they had been at the beginning of the illness. Sedative medication for insomnia has been used. Constipation has been marked and began just before the onset of the narcolepsy. He has had frontal headache for several years when he strains his eyes (reading, watching motion pictures). There has been a gain of 30 pounds in weight during the past six years. The weight at examination was 190 pounds.

Physical examination revealed nothing remarkable. He had the appearance of an exceptionally rugged youth, large of frame and only moderately obese.

The urine was normal. The blood count showed a mild eosinophilia (8 to 9 per cent) but was otherwise normal. Chemical and serological examinations of the blood were normal. The basal metabolic rate was plus 4 per cent in the first test, and minus 15 per cent and minus 20 per cent in two subsequent examinations. Roentgen-ray examination of the skull showed expansion of the diploë and hypopneumatization of the sinuses. The sella turcica measured 5 by 8 mm. and was regular in outline. The heart and lungs were normal.

Inhalation of benzedrine sulphate was used for two days and gave slight relief. Oral medication, 10 mg. three times a day, has been followed by marked improvement, although there is still some drowsiness when he is inactive. He states that he can now read for several hours at a time, whereas before treatment was begun he fell asleep a few minutes after beginning to read. Insomnia is much less troublesome, but he still has occasional unpleasant dreams.

Summary

Our experience with narcolepsy supports the statement that the disease may occur at any age and that in the majority of cases it begins before age

Tabular Summary of Important Findings in Six Cases of Narcolepsy

Case, Sex, Age	Narcolepsy						Cataplexy		Treatment				Miscellaneous Findings				
	Age at Onset	Duration in Years	Length of Attacks	Aggravation	Prodromes	Automatic Actions	Length of Attacks	Exciting Cause	Ephedrine	Benzedrine			B.M.R.	Dreams	Irritability	Obesity	Constipation
										Inhalation	Orally	Toxicity					
I M.F. ♀ 52	49	3	Few seconds to several minutes	Monotony; after meals; morning; cold days; very warm room	Diplopia and dull feeling in eyes	At times	Few seconds or minutes	Hearty laughter; excitement	Slight relief	Not used	Complete relief	Possibly aggravation of existing gastric symptoms at first	−24%	Unpleasant; insomnia (relieved by treatment)	Yes	Moderate, especially since onset of narcolepsy	No
II C.E.B. ♂ 17	10	7	Up to 1 hour at first; now only a few minutes	Monotony; warmth; fatigue	None	Writing; walking (has lost his way)	Few moments (none for 6 months; frequent at first)	Excitement; laughter	No relief	Not used	Complete relief	Anorexia for first few days	−24%	Many, some of them horrible. less troubled in last year. No insomnia	Yes	Obese before; tall since onset	No
III A.H. ♀ 16	10	6	10–20 minutes	Monotony; forenoon	None	Walking rarely	5–20 minutes	Hearty laughter; anger; fear	Moderate relief at first; later none	Moderate relief	Complete relief	None	−16% −22% −26%	"Horrible" at first; less recently	Rare	Gradual gain since onset of narcolepsy	Moderate
IV R.R. ♂ 32	17	15	Few seconds to several minutes	Monotony; inaction; warmth; 11 a.m.–2 p.m.; after supper	Momentary cloud in front of eyes	Frequent. Writing, driving, talking	Momentary (rare slight attacks)	Hearty laughter; sudden anger; excitement	No relief	No relief	Marked but not complete relief	Occasional slight nausea at first, taking tablets without water	−14%	Unpleasant; insomnia (relieved by medicine)	No	Slight	No
V P.S. ♀ 12½	4(?)	8(±)	Few minutes to several hours	Monotony; warmth; inaction	None	None	No cataplectic seizures		Not used	Slight relief	Almost complete relief with 50 mg.	Added mensis; feeling of fullness with meals	−23%	Not abnormal. Sleeps well	Marked	None	Marked
VI W.L. ♂ 22	14–15	7–8	Few seconds, rarely a few minutes	Monotony; warmth; afternoon	None	Walking frequently; other action rarely	Few seconds	Excitement; sudden anger; hearty laughter	Not used	Slight relief	Marked but not complete relief	None	+ 4% −15% −20%	Unpleasant; insomnia	Only when aroused	Moderate	Very marked, began just before onset of narcolepsy

twenty-five. All of our patients are especially prone to become sleepy under monotonous actions or influences. The early part of the day is particularly conducive to drowsiness in two of our cases, in two there is a post-prandial inclination, and one patient is more susceptible in the afternoon. In two cases there is no predilection as to time of day. Warm weather or a warm room is a factor in three cases. Two show no seasonal influence and one, contrary to general observation, is worse on cold days. Unpleasant dreams are recorded by four of the patients. Cataplectic seizures are present in five cases, but not in case 5, the youngest of the series. The basal metabolic rate in all of our cases is lower than the mean rate in the large series reported by Daniels.[3] The reason for this is not apparent.

Oral treatment with benzedrine sulphate has been followed by marked relief in all cases of our series. The effective daily amount of drug varied from 20 to 50 mg. Inhalation was tried in four cases, with slight benefit in case 5, moderate in cases 3 and 6, and none in case 4. It appears that the difference between inhalation and ingestion is quantitative. One patient complained of slight nausea at the beginning of oral medication, another's gastrointestinal symptoms were aggravated during the first period of treatment, but not subsequently, and a third had slight temporary anorexia at the beginning of each period of treatment. One patient, a colored girl, aged 12½, had an additional menstrual period while taking 50 mg. of the drug and has complained recently of a slight feeling of fullness at mealtime.

BIBLIOGRAPHY

1. New and Non-Official Remedies, 1935.
2. Prinzmetal, M., and Bloomberg, W.: The use of benzedrine for the treatment of narcolepsy, Jr. Am. Med. Assoc., 1935, cv, 2051.
3. Daniels, L. E.: Narcolepsy, Medicine, 1934, xiii, 1.
4. Trömner, E.: Narkolepsie (Schlafzwang), Zentralbl. f. d. ges. Neurol. u. Psychiat., 1929–30, liv, 326.
5. Rosenthal, C.: Zur Pathogenese, Ätiologie und versorgungsrechlichen Bedeutung der "genuinen" und post-traumatischen echten Narkolepsie, Arch. f. Psychiat., 1932, xcvi, 572.
6. Goldflam, S.: Zur Frage der genuinen Narkolepsie und ähnlichen Zustände, Deutsch. Ztschr. f. Nervenheilk., 1924, lxxxii, 20.
7. Grün, R.: Beitrag zur Kenntnis der Narkolepsie und der Frage der Dienstbeschädigung bei dieser Krankheit, Ztschr. f. d. ges. Neurol. u. Psychiat., 1931, cxxxiv, 155.
8. Beyermann: Über pathologische Schlafzustände, insbesonders narkoleptische Anfälle, in ihrem Zusammenhange mit Funktionsstörungen der Hypophyse, Ztschr. f. d. ges. Neurol. u. Psychiat., 1930, cxxviii, 726.
9. Redlich, E.: Die Gelineausche Narkolepsie, Med. Welt, 1927, i, 1281.
10. Thiele, R., and Bernhardt, N.: Erfahrungen über Narkolepsie, Zentralbl. f. d. ges. Neurol. u. Psychiat., 1931, lxi, 143.
11. Janota, O.: Symptomatische Behandlung der pathologischen Schlafsucht, besonders der Narkolepsie, Med. Klin., 1931, xxvii, 278.
12. Alles, G. A.: The comparative physiologic actions of the di-phenylisopropylamines: I. Pressor effect, Jr. Pharmacol. and Exper. Therap., 1933, xlvii, 339.

ABDOMINAL DISTENTION IN LOBAR PNEUMONIA *

By Joel Goldman, M.D., and Abraham Cohen, M.D., *Philadelphia, Pennsylvania*

In scanning the literature on meteorism we found a most interesting lecture, written by Francis Sibson [1] in 1873. We wish to quote from this classic.

> You will at once see how seriously distention of the colon must affect the organs of the chest, not only the lungs, but also the heart, by displacing that organ to the left, whereas, in the case of the stomach, its displacement tended rather to the right.
>
> We find that the heart and the lungs are put to an immense disadvantage—that the lungs are compressed and the reserved air driven out of them—that the heart is compressed and the blood driven out of it—that the ventricles are diminished in size and are incapable of receiving so much blood as they did before—that there is an obstacle to their action, and that they are incapable of sending out the blood that they have already received with the ease that they did before,—again, if you look at the walls of the chest and the diaphragm, you see what an obstacle is put to the very limits, by which, as it were, the lungs expand and the heart is moved. The cartilages of the ribs are pushed aside and lifted upwards. The cage of the chest has reached the limit of its power by the elevation given to it, and permanently given to it by the distention of the abdomen. Again look at the diaphragm, lifted up by this immense distention. How can it act downwards? If the diaphragm is affected by peritonitis, the inflammation paralyzes the inflamed muscle. The whole content is then narrowed to the smallest bounds; and the whole work of respiration must be done by the few ribs remaining unassailed at the top of the chest. In cases of peritonitis respiration is what is very well called high. The whole of the breathing is performed by the labored lifting up of the upper cartilages, the upper ribs and the clavicles—all the muscles that act—the sternocleido, the scalein, the levators of the ribs and the scapulae, are hard at work, and in spite of that, you see visible in the face that the patient is undergoing chronic asphyxia, and must soon die unless his breathing is relieved.

The Origin of Gases in the Intestinal Tract

We are not concerned here with the ordinary accumulation of gas in the intestinal tract, but with the excessive formation of gas which results in flatulent distention.

According to the work of Schoen, McIver, Redfield and Benedict,[2] the only gases of importance in distention are those which are not readily absorbed; hydrogen, nitrogen and methane. Other gases, however, may accumulate in the intestinal tract if their rate of formation exceeds their rate of absorption.

Cutting [3] believes that the origin of intestinal gas is three-fold: (1) decomposition of foodstuffs, (2) diffusion of gas from the blood stream, and (3) swallowed atmospheric air. He states that gases are produced

* Received for publication August 12, 1935.
From the Pneumonia Wards of the Philadelphia General Hospital.

by the action of bacteria on sugars in the lower portion of the small intestine and by the action of bacteria on any residue of cellulose which remains after digestion is complete. Free nitrogen occurs in the blood stream under a pressure of about four-fifths of an atmosphere, while oxygen and carbon dioxide occur in chemical combination. The nitrogen is free to leave the blood stream to replace other gases in the intestines when pressure relationships are favorable; whereas in order for oxygen or carbon dioxide to leave the blood stream, not only must pressure relationships be upset, but also conditions must be favorable for the liberation of these gases from their chemical combinations.

McIver [5] states that normally the amount of gas in the intestinal lumen is minimal because gases diffuse into the blood stream about as rapidly as they are formed. The presence of distention, however, indicates that formation has outstripped diffusion.

In his paper entitled "Constipation," Spencer [6] points out that the same laws apply in gas exchange between the blood stream and the intestinal lumen as apply to the gas exchange between tissues and blood, and blood and the pulmonary air. In speaking of flatulence he makes the significant statement that "whenever the condition can be anticipated, measures for precaution will prove more valuable than will measures for relief."

Alvarez [7] feels that flatulence with abdominal distention can become a serious complication during the course of pneumonia. He states that Boothby so far has had little or no trouble with flatulence in a series of patients with severe pneumonia treated in a chamber containing 50 per cent oxygen because in such an atmosphere more of the nitrogen in the bowel can diffuse out.

Wiggers [8] agrees with other writers that putrefactive and fermentative changes are of minor importance, compared to disturbances in the diffusion of gases. In addition embarrassment of the circulation results from mechanical interference with the splanchnic circulation or from compression of the heart through the diaphragm.

In summary, these authors believe that gaseous distention depends chiefly upon alterations in the interchange of gases between the gastrointestinal tract and the blood. The normal equilibrium may be affected by disturbances in the toxicity and motility of the gastrointestinal musculature, or by interference with the local circulation from various causes. Fermentative processes and aerophagia may be contributory factors. It has also been suggested that the diminished capacity of the lungs in pneumonia may be in part responsible for the distention which is commonly associated with this disease.

Numerous drugs have been utilized to combat distention, none of which are satisfactory in all cases. Saline cathartics or even hypertonic salt solution (Orr [14]) may be helpful. While various opiates have been used extensively, there is still a difference of opinion as to their effect upon the movements and tone of the intestine. Nothnagel [16] concluded that small

doses of morphine increased the tone of the intestine while large amounts decreased it. Uhlmann and Abelin [17] demonstrated that the reverse occurred in etherized rabbits and guinea pigs, and Plant and Miller [19] found that morphine and other alkaloids of opium produced a decided increase in tonicity. Eserine has been used with indifferent success for more than half a century. Pitressin and pituitrin stimulate contraction of the smooth muscle, and are sometimes very effective. Choline and acetylcholine have been shown by a number of investigators [22, 23, 24, 25, 26] to stimulate the gastrointestinal musculature. Others,[27, 28] however, have not obtained constant or conspicuous results with them.

Treatment by Suction Siphonage

In June 1933, Paine, Carlson and Wangensteen [29] described a form of continuous lavage of the duodenum through a nasal tube which was effective in relieving postoperative distention, nausea and vomiting, and they suggested that this form of therapy be employed following gastric, biliary tract, intestinal, and kidney operations. In our paper it is suggested that a modification of this apparatus be made use of in lobar pneumonia and other conditions accompanied by abdominal distention. Distention is a symptom of decided importance since through its mechanical effects and through the distress and fatigue it causes the patient it may well have a decided effect upon the mortality rate in pneumonia and other febrile diseases. We have found the treatment of distention by rectal suction siphonage safe, inexpensive and simple. The results obtained in a large group of patients with lobar pneumonia at the Philadelphia General Hospital are here presented.

From December 1, 1934, to May 20, 1935, 335 cases of lobar pneumonia (220 men and 115 women) were treated in the special fever wards. This hospital accepts only charity cases for treatment. In most of them the disease was far advanced at the time of admission, and, since they were from the poorer sections of the city, their powers of resistance were not of the best.

Of these 335 cases of lobar pneumonia, 129 or 38.6 per cent were clinically distended (39.5 per cent of the men and 36.5 per cent of the women). The distention was of sufficient degree to necessitate active therapy. In comparison, there were few other complications. Our experience indicates that abdominal distention is by far the most common complication of lobar pneumonia.

In previous years, distention had been treated by various accepted routine procedures. The results obtained were far from satisfactory. This year we have used a combination of the laxative action of saline cathartics with the mechanical action of continuous suction siphonage as described below.

Many of the patients entered the hospital with distention, while others developed it as the disease progressed.

The degrees of distention have been classified as follows: Grade 1 or minimal, Grade 2 or moderate, and Grade 3 or marked distention. A summary is shown in table 2.

Early in the series many patients with Grade 3 distention were selected for treatment by suction siphonage; as the treatment was found to be successful, earlier cases were selected until late in the series nearly all were Grades 1 and 2. As has been discovered by other workers, early distention responds to treatment much more readily than when far advanced. Grade 3 cases were, at times, most difficult to deflate and to keep deflated; on the other hand, distention in Grade 1 or 2 cases rarely recurred once they were successfully deflated. It was finally decided to start suction siphonage on all cases that showed the earliest signs of distention. These were easily controlled, and the deflation was maintained in practically all so treated. However, many cases admitted with Grade 3 distention were refractory.

Technic of Rectal Tube Suction Siphonage

The apparatus used is almost the same as that described by Paine, Carlson, Wagensteen,[29] and Paine and Phillips,[30] in the treatment of postoperative distention, nausea and vomiting by nasal catheter suction siphonage, with the exception that a soft rubber rectal tube (French [28]) has been substituted for the Levin duodenal tube. (Figure 1.)

The patient who has become distended is given cleansing soap suds enemas until the return flow is fairly clear or until a successful return of fecal material has been obtained. Usually one or two soap suds enemas are sufficient. For a successful deflation the feces must be liquefied since solid stools and hard fecal masses will block the rectal tube. A liquid stool is obtained by giving the patient, daily, one ounce of saturated magnesium sulphate solution. Once a liquid stool is obtained, the dosage of the saline laxative may be reduced. However, in dehydrated patients or in older individuals with fecal impactions, large doses of the drug may be necessary. Most of the failures occurred in patients with hard, impacted feces which were resistant to laxative action.

A soft rubber rectal tube is inserted from two to three inches into the rectum. If the tube is forced any farther into the rectum it will coil on itself, balloon out the rectum and give the patient a false rectal impulse (figures 2 and 3). The tube is lubricated with either vaseline or an astringent rectal jelly. The latter is used to allay the slight tenesmus which may appear in those cases which are under treatment for fairly long periods of time. The following is a description of the apparatus, quoted from Paine and Phillips.[30] In our apparatus a rectal tube is used in place of the nasal tube.

"The apparatus consists of two bottles with the capacity of four liters each. One bottle is hung inverted from an irrigation standard by a canvas sling or bag (or by a wire basket as shown in figure 1). The other bottle

is set on the floor at the foot of the standard. A two-holed rubber stopper with two glass tubes fits into the mouth of the inverted bottle. One of these tubes is short (about four inches long) and the other is longer (about 14 inches long) and extends almost to the bottom of the inverted bottle, that is, to the end which is uppermost as it hangs. A rubber tube connects

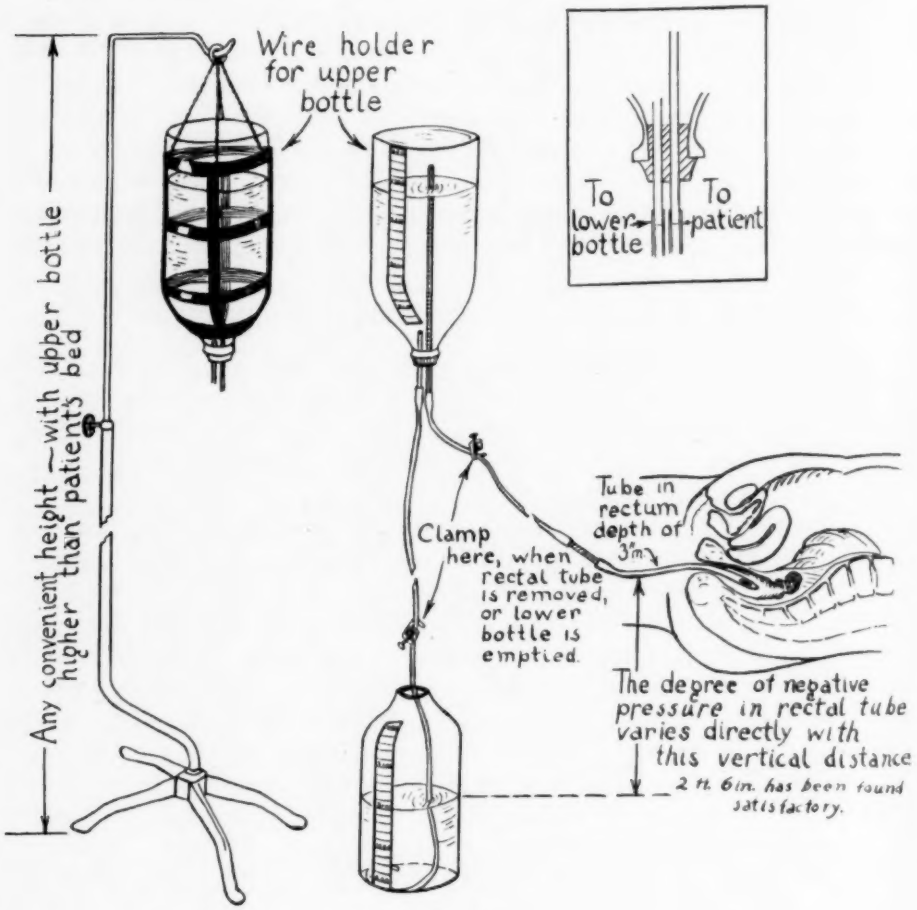

FIG. 1.

the longer glass to the nasal tube (or rectal tube), and another leads from the shorter glass tube to the bottle which is situated on the floor.

"To start the suction, the upper bottle is filled completely with cold tap water, and the rubber stopper with the tubing attached is put into place in the bottle neck. The rubber tubing leading to the longer glass tube is not yet connected to the nasal tube (rectal tube). Both rubber tubes are clamped off, and the bottle inverted and hung on a standard at a convenient height, about six feet from the floor. The end of the rubber tubing from the shorter glass tube is placed in the floor bottle, and enough water is added

to cover the end of the tube well. This point is very important in order that a closed system will be made and a constant suction insured. The clamps on the rubber tubing are then removed while a finger is held over the end which will later be attached to the nasal tube (rectal tube). If

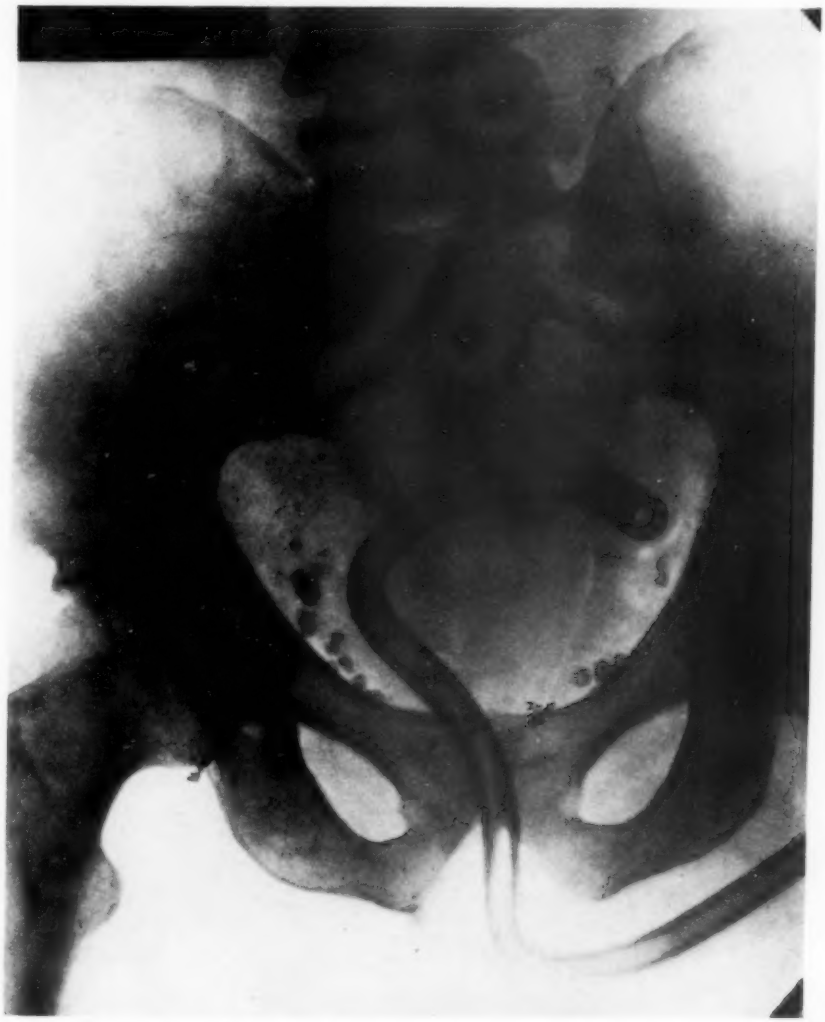

FIG. 2. A rectal tube inserted the wrong way.

suction is not immediately felt by the finger there is air in the tubing leading to the lower bottle. This can easily be removed by injecting a few cubic centimeters of water with a syringe into the tube which is connected to the longer glass tube. When suction is perceived, the tube is connected with the nasal tube (rectal tube)."

The return of gas and liquid feces is not measured for there is no

danger of dehydration as long as the urinary output is sufficiently high (from 800 to 1200 c.c. daily).

The rectal tube and the connecting rubber tubes are irrigated at least every four hours by forcing fluid through them with a syringe. If the

FIG. 3. A rectal tube inserted the right way.

tubes are blocked by fecal masses they must be thoroughly cleaned or replaced. The apparatus is sterilized by boiling when it is no longer in use.

The rectal tube is used only as long as is necessary to reduce the distention. If it is used excessively long there may be rectal irritation. If distention recurs it may be necessary to repeat the procedure. The continuous use of this method was not insisted upon. If the patient desired a

bed pan it was given to him. From time to time enemas were given. The criticism may logically be offered that the enemas may have relieved the distention, but we have seen hundreds of cases in which they did not.

Pituitrin was found to be nearly ineffectual in stimulating peristalsis in these cases, but Pitressin did help occasionally. No other drugs were used to assist in combating the distention.

The only untoward effect noted after the prolonged use of the rectal tube was tenesmus. This occurred chiefly in those patients who had previously existing internal hemorrhoids, and was easily alleviated by the use of an anesthetic astringent rectal jelly. No rectal bleeding was noted.

The above described procedure has been very successful in combating the abdominal distention of lobar pneumonia. We are presenting the results of such treatment in 100 unselected cases. The following table summarizes the duration of the lobar pneumonia when treatment was first instituted.

TABLE I

12 to 24 hours	2 to 4 days	4 to 6 days	Longer than 6 days
12 cases	23 cases	25 cases	40 cases

It will be noted that 65 per cent of these cases were seen relatively late, four days or later, in the course of the pneumonia. Of these, the degree of distention was as follows: Grade 1, 7 cases; Grade 2, 53 cases; Grade 3, 40 cases.

The length of time the rectal tube suction siphonage was used is shown in table 2.

TABLE II

	12 to 24 hrs.	2 to 4 days	4 to 6 days	Longer than 6 days
Successfully deflated.....	69 cases	6 cases	3 cases	9 cases
Partially deflated—6 cases		*Total*—87% successfully treated; 6% partially successfully treated; 7% complete failure.		
Unsuccessfully treated—7 cases				

Most of the cases were controlled within 24 hours, only 18 per cent of the successfully treated cases requiring a longer period for control. The partially deflated and unsuccessfully treated were treated over an indefinite period before being discontinued. It was in these 13 per cent that the rectal irritation occurred.

The rate of death and recovery of these cases is as follows:

TABLE III

	10 to 19 yrs. old	20 to 29 yrs. old	30 to 39 yrs. old	40 to 49 yrs. old	50 to 59 yrs. old	60 to 69 yrs. old	70 to 79 yrs. old	80 to 89 yrs. old
Lived	8	10	16	18	4	4	0	0
Died	1	8	8	6	8	6	1	2
Total	9	18	24	24	12	10	1	2

Total died..... 40%
Total lived..... 60%

It was noted that in 34 per cent of these cases the distention was completely controlled without influencing the fatal termination of the disease. In only two cases unsuccessfully treated did the distention seem to be a direct cause of death. However, we believe that the distention was a true indication of the degree of toxemia present, the severest distention invariably occurring in the most toxic patients.

In addition to the actual deflation the procedure has been of great value in other ways. Our patients have received more rest (the prime requisite in any régime of treatment for lobar pneumonia) than they did before the introduction of this treatment. The patient does not need a bed pan frequently, and there is no straining to add to the load of a weak heart. We have had patients so treated who have not needed a bed pan for 96 hours during which they were perfectly at rest. The procedure has been especially helpful in this respect in the case of patients treated in oxygen tents. The nursing problem is simplified by lesser need of moving the patient. Incontinence of feces occurred only twice in the 100 cases reviewed. Our experience with the practical application of this method of treatment makes us feel that it is very well adapted to use in the home as well as on the hospital wards.

CONCLUSIONS

1. Abdominal distention is the commonest complication in lobar pneumonia. When extreme it may be a contributory factor in the mortality rate.

2. Rectal suction siphonage is a safe, inexpensive, and effective method of relieving abdominal distention, and has been a great comfort to our patients.

The authors wish to express their appreciation to Miss Blanche Loeb Langsdorf for her valuable assistance in collecting statistics for this paper.

REFERENCES

1. SIBSON, F.: Brit. Med. Jr., August 2, 1873.
2. SCHOEN, MCIVER, REDFIELD, and BENEDICT: Am. Jr. Surg., August, 1933.
3. CUTTING, R. A.: Principles of preoperative and postoperative treatment, Am. Jr. Surg., 1931, xii, 561.

4. Von Bungle: Lehrbuch der Physiologie des Menschen, 2d Ed., 1905, F. C. W. Vogel, Leipzig.
5. McIver, M. A., Redfield, A. C., and Benedict, E. B.: Gaseous exchange between blood and lumen of stomach and intestines, Am. Jr. Physiol., 1926, lxxvi, 92–111.
6. Spencer, H. J.: Constipation, Am. Jr. Digest. Dis. and Nutr., 1935, ii, 7–13.
7. Alvarez, W. C.: The mechanics of the digestive tract, 2d Ed., 1929, Paul B. Hoeber, Inc., N. Y., p. 34.
8. Wiggers, C. J.: Physiology in health and disease, 1934, Lea and Febiger, Philadelphia.
9. Kantor, J. L., and Marks, J. A.: Study of intestinal flatulence, Ann. Int. Med., 1929, iii, 403–422.
10. Ogle, J. W.: Lancet, July 9, 1887.
11. Hicks, Braxton: Trans. Obst. Soc., 1869.
12. Allbutt, Clifford: Practitioner, 1869.
13. Broadbent, W. H.: Cases of paralysis of cranial nerves, Brit. Med. Jr., 1879, ii, 87–89. A case of intestinal obstruction successfully treated by puncture of the small intestine, ibid., ii, 490.
14. Orr, T. G.: Treatment of postoperative "gas" pains, Ann. Surg., 1931, xciv, 157.
15. Henjeres, A. W.: Postoperative tympanites, New York State Med. Jr., 1931, xxxi, 74.
16. Nothnagel: Über die Einwirkung des Morphin auf den Darm, Arch. f. path. Anat., 1882, lxxxix, 1–8.
17. Uhlmann, F., and Abelin, J.: Beiträge zum Opiumproblem, Ztschr. f. exper. Therap., 1920, xxi, 58–96.
18. King, C. E., and Church, J. G.: Motor reaction of muscularis mucosae to some drugs, Am. Jr. Physiol., 1923, lxvi, 428–436.
19. Plant, O. H., and Miller, G. H.: Effects of morphine and other opium alkaloids on muscular activity of alimentary canal, Jr. Pharm. and Exper. Therap., 1926, xxvii, 361–383.
20. Oliver, G., and Schäfer, E. A.: On the physiological action of extracts of pituitary body and certain other glandular organs, Jr. Physiol., 1895, xviii, 276–279.
21. Weiland: Zur Kenntnis der Entstehung der Darmbewegung, Arch. f. d. gesammt. Physiol., 1912, cxlvii, 171–196.
22. Grossman: Über die klinische Brauchbarkeit des Cholins, München. med. Wchnschr., 1920, lxxii, 251.
23. Guggenheim and Loefflers: Über des Vorkommen und Schicksal des Cholins im Tierkorfer, Biochem. Ztschr., 1916, lxxiv, 208.
24. Dale, H. H.: Action of certain esters and ethers of choline, Jr. Pharm. and Exper. Therap., 1914, vi, 147–190.
25. Wolfe, C. G. L., and Canney, J. R. C.: Treatment of ileus by choline, Lancet, 1926, i, 707–709.
26. LeHeux, J. W.: Cholin als Hormon der Darmbewegung; über den Einfluss des Cholins auf die normale Magen-Darmbewegung, Arch. f. d. gesammt. Physiol., 1921, cxc, 301–310.
27. Carlson, A. J., Smith, E. A., and Gibbens, I.: Action of choline on alimentary canals of intact dogs, Am. Jr. Physiol., 1927, lxxxi, 431–435.
28. Ochsner, A., Gage, I. M., and Cutting, R. A.: Value of drugs in relief of ileus, Arch. Surg., 1930, xxi, 924–958.
29. Paine, J. R., Carlson, H. A., and Wangensteen, O. H.: Postoperative control of distention, nausea and vomiting, Jr. Am. Med. Assoc., 1933, c, 1910–1917.
30. Paine, J. R., and Phillips, E. C.: Nasal catheter suction-siphonage, Am. Jr. Nursing, 1933, xxxiii, 525–533.

THE RÔLE OF ACCIDENTAL PUNCTURE OF VEINS IN THE PRODUCTION OF ALLERGIC SHOCK *

By G. L. WALDBOTT, M.D., F.A.C.P., and M. S. ASCHER, M.D.,
Detroit, Michigan

IN spite of many publications on the prevention of allergic shock following injections of pollen and serum, there remains a great deal of uncertainty concerning its causes and prevention. This is well illustrated by the fact that even those clinicians who are most experienced in the administration of hypodermic medication are still completely at loss to explain certain reactions. Piness,[1] for instance, stated, in 1934, that despite the most careful gauging of doses there are reactions for which we are unable to account.

The importance in this connection of accidental intravenous injection of the allergen is not sufficiently stressed. In a paper dealing with the prevention of reactions, Rudolph and Cohen [2] fail to emphasize the rôle of accidental puncture of veins in the production of reactions. Others (Duke,[3] Insley [4]) have proposed valuable measures to prevent shock, but do not propose means practicable for the general practitioner to prevent accidental intravenous injections. Commercial houses marketing serum and pollen extracts have greatly neglected to stress this feature in their directions to physicians. Yet, with few exceptions, the accidental intravenous administration of serum or pollen accounts for the fatal outcome in most cases of sudden death reported in the literature following injections.[5] It will be shown below that this constitutes a great menace in the giving of pollen injections.

Within the past few years we have been able to reduce the incidence of reactions from pollen injections to a marked degree by observing certain precautions outlined elsewhere.[6] These measures take into consideration the fact that severity of a reaction depends upon the state of sensitivity,† the rapidity of absorption of the antigen, and the degree of the overdose. In addition to an actual overdose due to error, to incorrectly judging the patient's degree of sensitivity or to switching from an old to a new extract, the following factors may contribute to the effect of an overdose: Simultaneous absorption of the same or another antigen to which sensitivity exists, by either the intestinal route (food), the respiratory route (pollen), or from the site of previous injections, or simultaneous absorption of bacterial materials from an infection present in the system.

Regardless of these precautions which were directed toward prevention of an overdose, reactions occurred, and, as a rule, were decidedly more

* Received for publication June 29, 1935.

† Whether this sensitivity is inherited (atopic) or acquired ("anaphylactic") does not alter in the slightest degree the symptomatology of shock.

severe than those formerly encountered. During the past hay-fever season we made observations concerning the relative frequency of accidental puncture of small venules, the diagnostic features connected with a reaction so produced, and the best methods of avoiding such mishaps.

Diagnostic Considerations

A puncture of a vein may result in two clinically distinct types of reactions, depending upon whether the extract is injected directly into the blood stream ("intravenous" reaction) or seeps into a small punctured venule soon after the injection ("backseepage" reaction).

1. *Intravenous Reactions.* The characteristic features of this type of reaction are the unusual severity of the manifestations and the absence of a local swelling at the site of injection. In a reaction due to inaccurate dosage, no matter how large the overdose may have been, there is always a time interval of a few minutes during which a more or less marked wheal arises on the site of injection. Often a reddened, more or less itchy, area can be noted along the lymph channels, similar to that seen in lymphangitis, before generalized urticaria and respiratory symptoms occur. In an "intravenous" reaction proper, skin manifestations are usually of little moment throughout. There is a decided prevalence of internal manifestations, particularly, of symptoms which can be attributed to edema of the lungs, and probably, of the liver. This is well in accord with Kahn's [7] recent observations that in shock produced in animals by the intravenous route there are considerably less skin-reacting antibodies present than if the shock-producing injection is made subcutaneously. Another distinctive feature is the absence of allergic symptoms after the reaction is controlled. While in "non-intravenous" reactions urticaria and other allergic symptoms may recur several hours after their control by epinephrine, an "intravenous" reaction produces its full effect immediately; little, if any, after-effect is noticeable with the exception of a generalized weakness or a low-grade pulmonary infection. This latter condition has been explained as due to secondary infection of residual areas of pulmonary edema (Waldbott and Snell [8]). The following is an instance of an "intravenous" reaction:

Case 1. J. K., a 17 year old hay-fever patient, had been successfully treated in 1932, in one of the dispensaries with which we are connected. He had the eighteenth injection of 1933, consisting of 10,000 units each of small and giant ragweed and cocklebur on July 7. On July 14, at 10:01 a.m., he received 12,000 units of the same pollen extracts. Within 20 seconds following the injection, he noticed a strange taste in his mouth, "tingling around the heart," and difficulty in breathing. Ten seconds afterwards he collapsed and became pulseless. A tourniquet was immediately applied by the attending nurse and 0.5 c.c. of epinephrine was given subcutaneously (10:03). The same amount was repeated at 10:05 by Dr. S. R. After the second injection of epinephrine the pupils reacted slightly to light and consciousness was regained for about three minutes. The pulse was not palpable at the time. At 10:08, 1.0 c.c. of epinephrine was given intramuscularly. The pulse became noticeably stronger and the respirations assumed a more regular character. From 10:03 to

10:55 the tourniquet was loosened only three times for a period of a few moments, and entirely removed at 10:55. Outside of the usual effect of epinephrine and an unusual degree of general weakness which lasted for several days there were no noticeable allergic symptoms after the incident. There was no urticaria, either localized or generalized. Not the slightest local reaction was present at the site of injection. Although no further treatment was given during the balance of the hay-fever season, the boy remained free from hay-fever.

Comment. One is particularly impressed first with the unusual severity of the clinical manifestations, resulting in this case in complete pulselessness; and second with the absence of urticaria and local swelling, and of any material after-effect. We feel that in this case the life of the patient was saved by the immediate administration of large doses of epinephrine, and that the application of the tourniquet was of no avail.

CHART I
Differential Features of Intravenous Reactions

	Overdose	"Backseepage"	"Intravenous"
Premonitory Evidence:	Rapid appearance of local wheal.	Bleeding at site of puncture or bloody suffusion.	
Local Reaction:	Speed of appearance and size of wheal indicates severity.	Occasionally bloody suffusion under skin.	None.
Time Interval:	Proportional to amount of overdose (5 minutes to 2 hours).	Between one to five minutes.	10 to 30 seconds.
Symptoms: Urticaria:	Marked.	Extreme at onset.	Little, if any.
Respiratory:	Hay-fever, bronchitis, asthma.	Hay-fever, bronchitis, asthma.	Pulmonary edema.
Collapse	Negligible.	Marked.	Extreme.
Others:	Flare-up of previously existing allergic or non-allergic foci.		Prostration, cyanosis.
Duration:	Prompt control by epinephrine. Urticaria may recur.	Symptom-free after control.	Generalized malaise for several days.
After-Effects:	Relief of allergic symptoms unless the overdose too drastic.		Broncho-pneumonia may ensue.
Response to *Treatment:* Epinephrine:	Promptly to 1/10 to 3/10 c.c., repeated if symptoms recur.	Larger doses (0.5 to 1.0 c.c.) needed immediately.	
Tourniquet:	Useful. In extreme cases incision of site of injection.	Useful.	Of no avail.

2. *"Backseepage" Reactions.* While to our knowledge only four truly "intravenous" reactions were encountered within the past three seasons in a series of 41,037 injections, there is another more common source of dangerous reactions, which has not been sufficiently emphasized: i.e., the puncture of a vein and backseepage into the blood stream. This occurred 34 times in this series. In the hypodermic administration of pollen and serum, it is relatively common that a small venule or capillary is punctured. Should any of the injected material ooze into the punctured venule, the reaction resulting would be similar to that of a true "intravenous" reaction. This type of reaction can usually be recognized by the following evidence: Presence of blood on the site of injection or a bloody suffusion under the skin which becomes rapidly replaced by a wheal. Generalized allergic symptoms occur within one to five minutes and are unusually severe. They consist of both cutaneous and internal manifestations, in contradistinction to the true "intravenous" reaction where skin manifestations are either absent or slight. Dermal edema is intense and can often be seen to spread rapidly from the site of injection over the entire body surface. Collapse occurs within a few minutes if the reaction is severe or not immediately controlled. Since instituting the precautions mentioned below, the incidence of these reactions has been reduced but not entirely eliminated. Chart 2 is a tabulation of the incidence of the different types of reactions; chart 1 presents their differential diagnostic features.

CHART II
Incidence of Reactions Encountered During 1932–1934

Year	Number of Injections	Reactions Encountered					
		Total Number	Incidence	"Intravenous"	Incidence	"Backseepage"	Incidence
1932	9898	36	1 : 276	1	1 : 9898	11	1 : 899
1933	12364	44	1 : 280	1	1 : 12364	14	1 : 883
Total 1932–1933	22262	80	1 : 278	2	1 : 11131	25	1 : 890
1934	18775	61	1 : 308	2*	1 : 9387	12	1 : 1564

* Only a small portion of the extract was injected since the accidental puncture of the vein was recognized during the injection (repeated retraction of plunger of syringe).

EVALUATION OF THE CUSTOMARY MEASURES OF CONTROL

The measures which have been advocated for the control of reactions from pollen extracts are the application of a tourniquet above the site of injection and the administration of epinephrine.[3, 4] Recently, Rice [9] demonstrated that the absorption of epinephrine may be controlled similarly to

that of the pollen extract by applying a second tourniquet above the site of the injected epinephrine. In extreme cases incision of the site of injection after the application of a tourniquet above may be resorted to.*

These measures, although they are entirely satisfactory for reactions due to overdose, in our experience have proved inadequate to prevent reactions due to puncture of veins. Duke [3] considered the accidental puncture of venules when he advocated the administration of epinephrine and ephedrine simultaneously with a small portion of the pollen extract. Only after noting a preliminary subcutaneous blanching does he inject the remaining amount. There are two definite disadvantages to this procedure: First, these drugs delay or prevent the occurrence of a local swelling which serves as a gauge for subsequent injections and thus make further treatment more difficult. Second, there is the well-known effect of even small doses of epinephrine which has often discouraged patients from continuing further treatment.

CHART III
Comparison of Potential and Actual Reactions in 1934
(In 18,775 Injections)

	Number	Incidence
Blood in Syringe: (Retraction of plunger)	12	1 : 1564
No. Times Blood on Cotton	104	1 : 180
"Intravenous" Reactions	2	1 : 9387
"Backseepage" Reactions	12	1 : 1564

PREVENTION OF "INTRAVENOUS" AND "BACKSEEPAGE" REACTIONS

If for these reasons, one does not wish to avail himself of Duke's method, the following precautions are suggested for the prevention of reactions due to puncture of a vein:

1. Care in selecting an area for injection which is not highly vascularized. Such a suggestion may seem superfluous, had we not encountered patients in whom blood was noted on retracting the plunger on repeated occasions. In five cases this occurred more than twice in the same person and, in one individual, blood was recovered on four different occasions. After a more careful inspection of the skin we were able to discern small veins which had been punctured and which we had previously overlooked. We are now in the habit of inspecting the prospective area very carefully, paying attention to good lighting conditions, and having the patient open and close the fist after the venous return had been compressed manually

* The value of the last mode of treatment is well illustrated by the following case: In a patient (E. P.) an extreme overdose of cotton extract had been given because of an incorrect estimation of the patient's degree of sensitivity. Within two minutes after the injection a markedly itching area had arisen and generalized symptoms seemed imminent. Upon incision of the wheal after a tourniquet had been applied above the site of injection, most of the extract mixed with blood was recovered and relatively little epinephrine was required to prevent disagreeable after-effects.

above the elbow. The injections are given in the subcutaneous regions of the extensor surface of the forearm, in order that sufficient space for the application of a tourniquet and the administration of epinephrine be available.

2. Repeated withdrawal of plunger. This precaution, we feel, constitutes a definite aid in the prevention and control of intravenous reactions. As shown in chart 3, there were 12 occasions in a series of 18,775 injections during the course of which blood appeared in the syringe. In two different instances blood was noted only after the second or third retraction of the plunger and after a small portion of the extract had been administered. This was apparently due to the fact that the needle was displaced after its first insertion into the skin. Although the needle was immediately withdrawn, the ensuing reactions were unusually severe. How small a fraction of a routine dose may thus account for rather alarming symptoms can be seen from the following instances:

Case 2. Mr. A. M., a pollen asthmatic undergoing perennial treatment, had reached 7200 units of both small and giant ragweed on July 26. On August 2, he was to receive 7500 units of the same pollen extracts. After a preliminary withdrawal of the plunger, after only about one-fifth of the contents of the syringe had been administered, a second withdrawal of the plunger disclosed blood in the syringe. The needle was immediately withdrawn. Almost immediately the patient noticed a marked burning sensation in the abdomen and about the mouth. He became extremely short of breath. In the meanwhile, he was given 1.0 c.c. of epinephrine and a tourniquet was applied above the site of injection. Marked cyanosis and collapse ensued. At that time a slight edema of the face was noted. A second injection of epinephrine, 1.0 c.c., was given subcutaneously. After three minutes he regained consciousness, his breathing became easier, and within a short time no symptoms were noticeable other than those attributable to the effect of epinephrine.

Case 3. Dr. E. J., a 52 year old pollen asthmatic, was to receive an injection of 10,000 units of small and giant ragweed on July 24. The needle was inserted and the plunger withdrawn without noticing any blood in the syringe. After only a few drops of the extract had been injected, a second withdrawal of the syringe disclosed blood in the syringe. The needle was immediately withdrawn, a tourniquet applied above the site of injection. Within 45 seconds the patient complained of a spastic contraction of his chest, followed by marked wheezing and dyspnea. Epinephrine (0.5 c.c.) had already been given by this time. No dermal manifestations or collapse occurred. The reaction gradually subsided.

At several occasions it was found that in spite of repeated retractions of the plunger, no blood was noted in the syringe even though a venule had evidently been punctured. The plunger used was obviously not sufficiently tight-fitted. We, therefore, replaced the syringes with asbestos-wrapped pistons by syringes with more tight-fitting glass plungers for the administration of pollen extracts. We feel that this has contributed to the reduction of the incidence of this type of reaction.

3. Watching the area of injection for blood. Another means of recognizing a punctured vein is the appearance of blood at the site of injection. While the presence of blood does not always indicate an imminent reaction, a precautionary small dose of epinephrine (0.2 c.c.) and the application of

a tourniquet will largely obviate the danger of a "backseepage" reaction, considering the fact that there is always a time interval of from one to five minutes before "backseepage" reactions occur.

4. Tight pressure upon the injected area. It is impossible to furnish data to prove the effectiveness of this procedure, but it is felt that it tends to prevent the occurrence of "backseepage" reactions by occluding through pressure small venules which might have been punctured.

5. Epinephrine. It may seem that the measures suggested here are concerned with the prophylaxis of reactions due to punctured veins rather than with their treatment. Since the outcome of the treatment depends entirely upon the rapidity with which epinephrine can be administered, the early recognition of this type of reaction is of the utmost importance.

Every patient should be instructed about the symptoms of "intravenous" reactions. If there is the slightest suspicion of the puncture of a vein, 0.2 to 0.3 c.c. of epinephrine should be given immediately. If the symptoms of an impending reaction should then ensue, the first injection of epinephrine should immediately be followed by a larger amount (0.5 to 1.0 c.c.) of epinephrine.

While these observations were made on patients receiving pollen extracts, they are applicable to injections of serum or of any other antigen to which unusual sensitivity exists.

Discussion

It may seem unusual that small amounts of intravenously-administered pollen extract are of such significance in the production of severe reactions inasmuch as Lichtenstein [10] has shown that pollen treatment can be given by the intravenous route. In his procedure, however, he was required to give initial doses, which were much smaller than is customary in ordinary treatment, and thus he probably built up a specific protection for this type of treatment. If, as Kahn's [7] work suggests, in intravenous therapy a different type of antibody is prevalent, one may assume that hyposensitization treatment by the subcutaneous route does not produce the protection required for intravenous treatment, and vice versa.

Concerning the medico-legal aspect of this problem, the liability to which physicians are susceptible in pollen therapy should be pointed out, if they have not available for immediate use a fresh solution of epinephrine. Some physicians have their nurses administer the injections of pollen and serums. Others make it a practice to allow their patients to administer the injections themselves, especially those who have been in the habit of giving themselves epinephrine. An emphatic warning must be given against such practice. The neglect to observe the patient for at least five to ten minutes after the injection is another matter, which, in our opinion, may involve legal entanglements. As pointed out, the reactions due to "intravenous" administration occur within a relatively short interval, and, moreover, the beginning of a reaction due to an overdose will become noticeable within that period of time, by the appearance of an unusually marked local edema.

Summary

1. In the treatment with pollen extracts, the accidental puncture of veins and administration of the extract into the blood stream constitutes a grave emergency.

2. In 41,037 injections, 38 such reactions were encountered, 4 of which were due to direct introduction of the extract into the blood stream ("intravenous" reactions). The remaining were "backseepage" reactions due to subsequent flow of the extract into a previously punctured venule.

3. A clinical differentiation of true "intravenous" and "backseepage" reactions from those due to an overdose is outlined.

4. Only a small fraction of the routine dose, if accidentally introduced into the blood stream, is necessary to cause unusually severe symptoms.

5. The measures usually advocated for the prevention and treatment of reactions are discussed as adapted to reactions due to punctured veins. The following additional suggestions for their early recognition and control are presented: Care in avoidance of visible veins in the selection of the site of injection; repeated withdrawal of the plunger before and during the injection for evidence of blood; watching the site of injection for subsequent bleeding and subcutaneous hemorrhage; and pressure upon the site of injection.

6. The rapidity with which epinephrine is given determines the course of the "intravenous" and "backseepage" reactions. The application of a tourniquet is an aid in controlling a "backseepage" reaction, but is of no avail if the pollen extract has been injected directly into the vein.

7. In contrast to an incidence of one "backseepage" reaction in 890 injections, only one such reaction in 1564 injections was noted in 1934 since instituting the above precautions. In the two instances of "intravenous" reactions, only a small portion of the routine dose was administered due to early recognition.

BIBLIOGRAPHY

1. Piness, S.: Discussion, Jr. Allergy, 1934, vi, 99.
2. Rudolph, J. A., and Cohen, M. B.: Types of human hypersensitiveness, their relationship to liability to serum reactions, Jr. Am. Med. Assoc., 1934, cii, 900.
3. Duke, W. W.: New method of administering pollen extract for purposes of preventing reactions, Jr. Am. Med. Assoc., 1930, xciv, 767.
4. Insley, S. W.: The control of immediate shock following hypodermic medication, Jr. Am. Med. Assoc., 1930, xciv, 765.
5. Waldbott, G. L.: The prevention of anaphylactic shock, Jr. Am. Med. Assoc., 1932, xcviii, 446.
6. Waldbott, G. L.: Systemic reactions from pollen injections, Jr. Am. Med. Assoc., 1931, xcvi, 1848.
7. Kahn, R. L.: Study on tissue reactions in immunity: comparative response following intravenous and intradermal injections of organisms, Jr. Immunol., 1933, xxv, 339.
8. Waldbott, G. L., and Snell, A. D.: Pulmonary lesions resembling pneumonia as the result of allergic shock, Jr. Pediat., 1935, vi, 229.
9. Rice, R. M.: Method of controlling pollen reactions, Jr. Am. Med. Assoc., 1934, cii, 1222.
10. Lichtenstein, M. R.: Intravenous pollen therapy, Jr. Allergy, 1934, v, 231.

SCHILLER, THE GREATEST OF THE MEDICAL POETS *

By Louis H. Roddis, F.A.C.P., Commander, Medical Corps, U. S. Navy

Johan Christoph Friedrich Schiller, the poet and friend of Goethe, was born November 10, 1759. November 10 was the birthday of another medical poet, Oliver Goldsmith, born 31 years before in 1728.

Schiller's place of birth was the little town of Marbach in Wurtemberg, Germany, situated in a district of the Rhine valley long famous for the beauty of its scenery and the richness of its agriculture. The eminent German soldier Von Hutten, known to medical men principally for his connection with the early history of syphilis, who spoke with authority for he had travelled in all parts of the Fatherland, said of Wurtemberg in a letter written in May 1517, " There is scarcely a more beautiful neighborhood in all Germany than the Province of Wurtemberg. The soil is excellent, the climate mild and wholesome, mountains, valleys, meadows, streams and forests interspersed in pleasing variety. The products of the earth are unusually abundant, the wine is like the country. The Suabians call Stuttgart the Earthly Paradise, so charming is the situation of the town." This encomium is well deserved. The pine clad slopes of the Black Forest bound it on the south, while vineyards, fields, villages, cities, cathedrals, and ruined castles along the Rhine and the Neckar add to the scenic beauty of the district and make it an idyllic homeland for a poet. Schiller's attachment to his home was deep and romantic, and this feeling exercised a powerful influence over his life and poetry.

The father of the poet had himself been apprenticed to a surgeon, and served in that capacity in the Bavarian Army throughout the campaigns in the Netherlands during the Wars of the Spanish Succession. Later he was commissioned as Ensign and Adjutant by the reigning Duke of Wurtemberg who, after the Peace of Paris, continued him in his service, advanced him to the rank of Captain and Major, and employed him as his chief forester. This was a task to which he was peculiarly suited as he had a great interest in forestry and landscape gardening. The remainder of his life was spent in the establishment of nurseries, the planting of trees and the improvement of the grounds at the Duke's beautiful forest castle " Die Solitüde " or " The Solitude." He is said to have planted and raised from seeds 60,000 forest trees. He published a book on forestry, and lived to enjoy the fame of his son. He was evidently a man of forceful character, practical, conscientious

* Received for publication December 2, 1935.

This is the seventh of a series of portraits of medical poets. Those which have previously appeared in the Annals of Internal Medicine are: Joseph Rodman Drake, February, 1929; Oliver Wendell Holmes, June, 1930; Oliver Goldsmith, May, 1932; Wm. Savage Pitts, January, 1933; Lieutenant Colonel John McCrae, June, 1933; Dr. Richard Shuckburgh, June, 1934.

and deeply religious. The mother had a less strongly marked personality though she was affectionate and devoted. While it has been the fashion to state that the remarkable qualities of so many great men were received from their mothers, it seems more than likely that in the case of Schiller much of his strength and ability were derived from his sire.

Fritz, as most German boys named Friedrich are called, received his first school instruction from Philip Moser, the Lutheran pastor at Lorch, for though born in southern Germany where Catholicism was the prevailing religion, Schiller's people were Protestants. It was the desire of the parents that their boy should enter the church, and indeed he seems to have had an inclination for it. We have a charming account, by one of his biographers, of Schiller as a boy of five or six years playing at being a pastor. He would tie one of his mother's black aprons about his neck in the manner of a surplice, put on a cap, and standing on a chair as a pulpit he would deliver a sermon, very serious about it all and much offended if anyone laughed at him.

The reigning prince of Wurtemberg was a petty tyrant, full of energy and bustle, who, after a life of extravagance and dissipation, proposed to devote the later years of his life to good works. One of his hobbies was a military academy at Stuttgart, and here was placed young Schiller to be educated at the expense of the prince. The boy, however, had no choice as to the course he should like but was compelled to study law though his parents desired him to study theology. He finally obtained permission to give up the law but only on the condition that he would study medicine. His entrance into our profession was, therefore, due to chance and necessity rather than to any interest in the subject.

The life of the students at the Academy was more like that of prisoners than scholars, and the strictest military formalities were observed. "It was a strange sight," says Nicolai (Travels Through Germany) who visited the Academy, "when at the dinner hour the pupils, in two columns, the nobles to the right and the burghers to the le. , filed solemnly into the dining hall without the slightest betrayal of pleasure so natural to boys at the sight of food. 'Front,' 'to the right,' 'to the left,' were called out as they reached the tables. When the command was given with a loud clap to say grace, all hands were folded, and, the prayer ended, each unfolded his hands, took hold of the chair to perfect time, pulled it out and sat down, just as a battalion of soldiers fire at command. Indeed, I am almost sure they kept time as they put their spoons into the soup."

It was in such an atmosphere that Schiller pursued his medical studies. His favorite reading was Luther's translation of the Bible, and Plutarch, and the German poets Lessing, Goethe, and Klopstock. The birthdays of the reigning prince and of prominent members of the court were celebrated by plays and musical festivals. Schiller wrote his first published poem for one of these occasions, printed in the Suabian Magazine, a local monthly periodical. In 1779 he produced a thesis "The Philosophy of Physiology," first

FIG. 1. JOHAN CHRISTOPH FRIEDRICH SCHILLER.

written in German and then translated into Latin. This essay did not receive the approbation of the authorities and Schiller was compelled to spend an additional year in study. The following is the Prince's comment to the Principal of the Academy: "I must confess there are some fine points in

pupil Schiller's essay and plenty of enthusiasm. But I do not wish it to be published and think it will be better for him to remain in the Academy another year until his enthusiasm has cooled off somewhat and then, if he continues to be industrious, he may become a great man." For once condescending mediocrity was right. Pupil Schiller did become a great man. The august and pedantic old prince did not realize that he really was a prophet.

The next year Schiller was more successful with his essay "The Connection of the Animal Nature of Man with the Spiritual." This was published as was a Latin dissertation required of him on inflammatory and putrid fevers.

He was now considered to have completed his professional training and was appointed Surgeon to the Regiment of Grenadiers, then in garrison at Stuttgart. As a free pupil at the Academy he was bound to the service of the reigning ducal house of Wurtemberg. Thus at 21 he found himself a military surgeon with a salary scarcely sufficient to support himself. He lodged with a former comrade at the Academy, Lieutenant Kapf, in a house in the Eberhards Strasse kept by a blond widow of 30, Frau Wischer or the "Vischerin." Kapf and Schiller shared a little room here which they referred to as "The Kennel." Here they occasionally entertained their bachelor friends with smoked sausage, potato salad and beer with plenty of tobacco smoke for a background. They had a soldier servant, Private Kronenbitter, with a uniform "adorned with patches." The poet Scharffenstein, who was a frequent visitor, describes Dr. Schiller as rigged in "a uniform of the old Prussian cut, rolls (which were intended for curls) on each side of his face, the military hat which was hardly large enough to cover his head and from under which hung his long thick queue. Around his neck he wore a stiff stock of horsehair."

During the later years at the Academy and the first months as an Army surgeon Schiller wrote his first great work, the tragedy called "The Robbers." The appearance of that poem and its almost immediate success on the stage soon made the 21 year old Army doctor famous throughout Germany. Scherr tells of his stealing away at this time from his duties without leave, accompanied by a comrade journeying to Mannheim to see a performance of his play, and "very near being too late, detained by the charms of a pretty barmaid on the way." "Happy carelessness of youth," says this biographer, "which, even on the threshold of a great event, could be stayed by the bright eyes of a barmaid."

The tyrannical old Prince of Wurtemberg did not approve of his Army surgeons becoming poets. He felt it was a waste of state education, and some of the liberal sentiments expressed in "The Robbers" were also not to his liking. Schiller was forbidden to publish any more poetry without first passing it through the hands of the censor. This and the fear of imprisonment led to Schiller's decision to flee from the service of the Prince and to devote himself entirely to literature. It was a decision which of

course separated him from any hope of official position in Wurtemberg and also separated him from medical practice, though to the end of his life he maintained considerable interest in medicine and on a number of occa-

FIG. 2. The statue of Schiller in Como Park, St. Paul, Minnesota.

sions when in isolated situations in the country he rendered professional services to persons in need of them.

Schiller's next great literary work was the drama of "Don Carlos" which further increased his fame and led to the beginning of his friendship with Goethe and Humboldt. He began also his historical studies and in 1789 he was called to Jena to become the Professor of History at that cele-

brated university. The next few years saw his reputation as a historian established by his "History of the Revolt of the Netherlands," the "History of the Thirty Years War," and his historical essays. He also became deeply interested in philosophy and aesthetics, and his essays in these fields such as that on "Grace and Dignity," and "The Aesthetic Education of Man" still further enhanced his fame. It is unfortunate that a long cherished project for a German biographical collection modeled on Plutarch was never begun.

In February 1790 Schiller married the younger of two sisters, Charlotte, or as she was generally called, Lotte Lengenfeld. Schiller's pet name for her was "Lolo." The older sister Caroline also loved him but later married her cousin William von Wolzogen. His marriage was an extremely happy one, as nearly ideal apparently as it was possible to be. In 1797 he purchased a comfortable home near Jena surrounded by a pleasant garden and with an admirable view. He wrote in the spring of that year to Goethe: "I salute you from my garden to which I removed today. A lovely landscape surrounds me; the sun is smiling with a friendly adieu and the nightingale is trilling. Everything around is cheerful and my first evening in my own house is of the happiest augury." This house stood on a gentle eminence at the end of a hedge-lined path called "Monks' Alley." Behind it on a slope of the hill was the garden full of flowers and vegetables planted together as was the custom in old-fashioned gardens. At the top of the slope was a clump of trees beyond which the ground fell away precipitously to the bed of the Leutrabach whose rushing waters could be heard below. At the top of the slope under a linden, a fir, and an acacia stood a little one room cottage which served as the poet's study. It is now torn down and a stone marked with the inscription "Here Schiller wrote his Wallenstein" indicates its former location. Beside it in an arbor was an old stone table where Schiller often sat when writing and where he often talked with Goethe. Here too he wrote many of his most famous lyrics including the "Song of the Bell," "The Glove," "The Hymn of Joy," "The Ring of Polycrates," and "The Dignity of Man." The dramas that followed, "Maria Stuart," the "Maid of Orleans," "William Tell," "Wallenstein," and the "Bride of Messina" placed Schiller among the greatest of the dramatic poets.

Though he had many love affairs before marriage Schiller was one of the most domestic types of men and was happiest in the enjoyment of his home and family life with his wife and four children. His literary success also gave him great pleasure. Both of his parents lived to see him recognized as one of the greatest poets of all time. But despite the happiness and satisfaction from these things his last days were clouded by ill health and financial worries. The latter were partly alleviated by a pension from the Duke of Weimar but work and pleasure were marred by frequent attacks of illness. The first of these attacks began in Jena in 1790 and was apparently a cholecystitis and hepatitis. Later attacks became more fre-

quent and severe and in the spring of 1805 a broncho-pneumonia as a complication ended his life. This was the year of Wagram and Trafalgar. He was but 45 years of age. As he was dying he replied to a question as to how he felt, "calmer and calmer." His widow and two sons and two daughters survived him. The news of his death, in the words of Carlyle, "Fell cold on many a heart; not in Germany alone but over Europe it was regarded as a public loss by all who understood its meaning." This well expresses the affection felt toward him by all ranks of society as a lover of human kind and a spokesman of the best and noblest feelings of humanity. He was beloved for these qualities as well as respected and admired for his genius. Modesty, uprightness, manliness, and love of liberty, and affection and devotion to friends and family were outstanding characteristics.

Physically he was tall and slender, blond, with abundant red hair. His countenance and head were fine and his expression and smile attractive and amiable. He usually held himself with almost soldierly erectness, a heritage in part of his earlier military training. In later years when walking by himself he often went with his eyes cast upon the ground so that he would often nearly pass acquaintances without speaking but when he heard their salutation "he would catch hastily at his hat and give his cordial 'Guten Tag.'"

Schiller's intellect was remarkable for power, clearness and comprehensiveness. The nobility of his nature is seen throughout his works which shine with his love of God, country, liberty, home, men, women, children, nature, and life. A patriot in the best sense of that abused word he was able in "William Tell" to interpret nationalism in Switzerland and Germany, and in the "Maid of Orleans" the national aspirations of France.

His relatively short life had been full of accomplishment. A quotation again from Carlyle furnishes the most suitable conclusion to this sketch of the greatest of the medical poets, of whom medical men and particularly military medical men should be especially proud:

"The kingdoms which Schiller conquered were not won from one nation at the expense of suffering to another, they were soiled by no patriot's blood, no widow's, no orphan's tear. They were kingdoms conquered from the barren realms of Darkness, to increase the happiness and dignity and power of all men, new forms of Truth, new maxims of Wisdom, new images and scenes of Beauty won from the 'void and formless Infinite,' a possession forever to all the generations of the Earth."

Bibliographical Note: Scherr, Life and Times of Schiller, written about 1860, can scarcely be spoken of too enthusiastically. It is a classic of biography, worthy to stand beside Lockhart's Scott or Boswell's Johnson. Other works of importance are Palleske (2 volumes), Carlyle (a short but striking character study and appraisal of Schiller's genius), and the highly interesting biography by his sister-in-law, Caroline von Wolzogen.

The picture of Schiller reproduced here forms the frontispiece of Scherr's biography. The statue, a very handsome one, stands in Como Park, St. Paul, Minnesota, and is from a photograph taken by the writer.

CASE REPORTS

FELTY'S SYNDROME; REPORT OF A CASE WITH NECROPSY FINDINGS *

By Robert H. Williams, M.D., *Nashville, Tennessee*

In 1924, Felty [1] reported five cases in which the chief disturbances were chronic arthritis, splenomegaly and marked leukopenia.

In 1932, Hanrahan and Miller [2] reported a case with characteristics closely resembling those of Felty's cases, for which a splenectomy was performed with benefit both objectively and subjectively.

In March 1934, Craven [3] added another case, likewise treated by splenectomy with improvement. Also in March 1934, Alessandrini [4] reported a similar case in which splenectomy was advised, but refused by the patient.

In April 1934, Price and Schoenfeld [5] reported a case with complete post-mortem findings.

Until the present, only nine cases with this unusual and interesting syndrome have been reported, and the case to be presented in this paper is, as far as can be determined, the second autopsy report of such a case.

F. R., a white male, married, chaplain, aged 54 years, was admitted to the Second Medical Service, December 1, 1933, with the complaint of migratory joint pain of 10 days' duration.

Family history was irrelevant. He was born in Ontario, lived in Boston for the past 37 years and was never in the tropics. No history was obtained of malaria, typhoid, scarlet fever, tonsillitis, chorea, or rheumatism before the present illness. He had had no serious illnesses and had always been in good health. Sore throats, colds and dental troubles have been rare. No symptoms had been present referable to the cardio-respiratory, gastrointestinal or neuro-muscular systems. For the past three years there had been nocturia, twice per night.

The present illness had begun with chilliness, feverishness and languor two months before admission. These symptoms had persisted, and 10 days before admission, following exposure to a cool breeze for 12 hours, there was an aching and swelling in the left hand, disappearing spontaneously after 16 hours. Two days later there were pain and swelling in the right ankle, which cleared up considerably after 12 hours. Three days later the left hand became quite weak but not very painful. The day before admission, the feet began to swell and were very painful. This was soon followed by pain and swelling of the left shoulder and right knee, the pain disappearing in 12 hours. On the morning of admission there developed severe pain on motion in the right elbow.

On examination, the patient was found to be well developed and nourished, with a richly tanned skin. The eyes, nose, mouth, throat and chest showed nothing remarkable. In the infraclavicular regions, there was slight dullness, bronchovesicular

* Received for publication September 6, 1935.
From the Mallory Institute of Pathology, Boston City Hospital.

breath sounds and a few crackles following cough. There was also slight dullness over the apices, posteriorly. The firm, smooth, sharp edge of the spleen was felt two cm. below the left costal margin. The liver was not felt. There was free motion of all joints, except the right elbow, with relatively little discomfort. Very slight distress was experienced in both ankle joints. The left hand and wrist were definitely swollen and showed slight pitting edema. There was slight pitting edema of the right hand. The right elbow was held in a slightly flexed position, and the patient could not achieve complete extension without suffering severe pain. There were no objective signs about this joint except limitation of motion. The right knee showed nothing remarkable. There was a small amount of fluid in the left knee, and the patella floated. Both feet from the ankles down showed slight increase in heat and definite pitting edema.

The patient stayed in the hospital for about seven weeks during which time the spleen remained palpable two cm. below the costal margins. The total white count ranged around 3000. Roentgenograms on admission showed cloudiness of the outlines of the right elbow joint and hypertrophic arthritis of both knees with effusion. Roentgen-ray of the sinuses showed clouding of the right antrum. Prostatic smear revealed no gonococci. Two electrocardiograms, a roentgen-ray of the chest, two aerobic and anaerobic blood cultures, two agglutination tests for *B. melitensis*, two stool cultures, several urine examinations and a Wassermann test were all negative.

BLOOD STUDIES

	WBC in thousands	Pml.'s	Eosinophiles	Myelocytes	Metamyelocytes	Young pml.'s	Lymphocytes	Monocytes	RBC in millions	Hgb.	Reticulocytes
12/ 2/32	3.2									83	
12/ 3/32	2.4		3				48				
12/ 5/32	2.2	48	1				51				
12/ 7/32	2.5	48	2				49				
12/18/32	2.3	44	2				54				
2/21/33	3.3	55		4	6	6	28	1	2.7	62	
2/23/33	2.1	45	1	2	5		43	1			
2/27/33	2.2	59	2		1	4	34		3.01	63	1
5/17/33	3.2	6	3	2	2	40	46	1	4.6	77	
6/20/33	4.9	3			2	35	58	2	4.3	90	
7/27/33	3.3	6				32	62		6.2	90	
12/21/33	4.8	49	2				34	0	4.3		0.5
5/23/34	3.6	32					65	3	4.8		
8/20/34	2.4	57	2	3	3	16	19		3.3		
8/21/34	2.2	40		3	4	21	29	1			2
8/22/34	1.6	9		9	1	47	20				
8/26/34	3.2	34		3	2	24	36				
8/27/34	2.9	12		2	3	49	28	1			

On tapping the left knee, December 9, 50 c.c. of yellow turbid fluid were obtained, the total proteins of which were 4.5, the non-protein nitrogen 29, sugar 124, polymorphonuclear leukocytes 60 per cent, eosinophiles 2 per cent, lymphocytes 2 per cent and monocytes 2 per cent. No organisms were found by smear or culture.

The patient's treatment consisted chiefly of salicylates orally, physiotherapy and free fluids. By December 17, he had obtained free motion in the right elbow and shoulder. By December 29, there were no joint symptoms except stiffness in the right shoulder and right elbow. During the last week, he was given mild exercise for the various joints. Preparations were made for him to convalesce in Florida.

During his stay in the hospital there was an elevation of the temperature from 99 to 100°, almost every evening, but never above 100.5°. The pulse likewise was elevated from 85 to 100.

Having been at home for two weeks, during which time he had an irregular evening fever, he developed a sore throat. He was admitted to the Haines Memorial Hospital where he showed extensive ulceration of the soft palate and tonsillar pillars. The ulcerations were shallow, covered with a thin, white exudate and appeared like those seen in agranulocytic angina. The total white blood cell count was 2500 of which 35 per cent were polymorphonuclear leukocytes. Following nucleotide treatment the count rose to 3500, with 70 per cent polymorphonuclear leukocytes, and the throat rapidly cleared, but in spite of continued nucleotide treatment the count soon dropped once more to 2500 with 35 per cent polymorphonuclear leukocytes.

February 21, 1934, he was admitted to the Thorndike Memorial Laboratory with the complaint of soreness and stiffness in his joints and a drop in weight from his average of 137 pounds to 118 pounds, 15 pounds of this having been lost in the five preceding months.

Upon this admission, there was noted a pallor of the palms of the hands and nail beds. The firm, non-tender edge of the spleen was still felt two cm. below the costal margin. The liver edge was not felt. There was slight enlargement of the inguinal lymph nodes. No abnormalities of the joints were noticed.

The blood findings were as follows: white blood cells 3,300, 55 per cent neutrophiles, 4 per cent myelocytes, 6 per cent metamyelocytes, 28 per cent lymphocytes, 1 per cent monocytes, 6 per cent young neutrophiles; red blood cells 2,700,000 and hemoglobin 62 per cent.

The basal metabolic rate, and the results of the phenolsulphophthalein kidney function test and of gastric analysis were found normal.

Sternal puncture, February 24, 1933, showed numerous normoblasts and nucleated red blood cells, some stem cells, only a few granulocytes and those mostly myelocytes, rare adult polymorphonuclear leukocytes, numerous megakaryocytes.

After eight days in the hospital, during which time there was no essential change, he was discharged to convalesce in Florida. He returned for a check-up, May 17, after having spent three months in the South, looking much improved. He had gained 21 pounds, had a deep tan, felt generally better but still had some pains in his joints though to a lesser extent.

Examination showed as the essential features: slight stiffness of the elbow joints and an easily palpable spleen two cm. below the costal margin. The red blood cells had risen to 4,600,000, but the white count was only 3,200.

The patient got along quite well and was relatively free of arthritic symptoms until about August 10, 1934, at which time he began to have fever and chills, followed in a few days by a productive cough. On August 20, he was admitted with symptoms and signs of bronchopneumonia in the left upper lobe which soon spread to all lobes. At no time did the white count rise above 3,200 in spite of the fact that 40 c.c. of nucleotide per day were given beginning August 24. The patient died on August 28.

An autopsy, restricted to the chest and abdomen, was performed two hours postmortem. The lymph nodes at the head of the pancreas and around the celiac axis were moderately enlarged, firm and uniformly light pinkish-yellow on cut section.

The visceral surfaces of the lungs were covered with a thin fresh layer of fibrin, and there were 400 c.c. of thin, straw-colored fluid in each pleural cavity. The left lung weighed 700 grams and the right 900 grams. All lobes were heavy, uniformly firm, very slightly crepitant and on cut section presented a uniform light gray, glistening surface, from which a small amount of seropurulent fluid could be scraped.

The spleen was moderately enlarged, weighing 260 grams. The capsule was smooth, gray and glistening and the pulp dark red, firm, smooth, relatively dry. The cut surface yielded little on scraping. The trabeculae and Malpighian corpuscles were not very distinct.

The liver was moderately enlarged, weighing 2000 grams. The capsular and cut surfaces were smooth, firm, light brown and showed the lobules fairly distinctly.

In the distal three feet of the colon were many diverticula, averaging 5 mm. in length and 4 mm. in width. The mucosa of some of the diverticula was injected though not ulcerated.

The bone marrow in the middle of the femur and in the tibia consisted of fat, whereas in the upper end of the femur it was yellowish-red. Sternal and lumbar marrows were grayish-red and firm. There was moderate lipping of the bodies of the vertebrae and an increase in density of the bone.

Microscopic examination of all lobes of the lung showed an advanced organization with a diffuse infiltration consisting of a moderate number of polymorphonuclear leukocytes though there were almost as many plasma cells, lymphocytes and macrophages.

The Malpighian corpuscles of the spleen were not very large or distinct. The sinuses were inconspicuous. The pulp was highly cellular, consisting chiefly of red blood cells, lymphocytes and plasma cells. There was also a moderate number of macrophages, a few nucleated red blood cells and rare stem cells. A few macrophages had phagocytosed red blood cells. Polymorphonuclear leukocytes were scarce. The liver showed extensive hydropic degeneration. There was a slight increase in lymphocytes and plasma cells in the sinusoids and a few Russell's "fuchsin bodies."

In one adrenal was a focus of plasma cells, lymphocytes and macrophages.

Sections of the tracheal and mesenteric lymph nodes showed an obliteration of the normal architecture by the diffuse infiltration with plasma cells. There was a moderate number of macrophages and Russell's "fuchsin bodies" and a few stem cells and myelocytes irregularly scattered. Some of the macrophages had phagocytosed lymphocytes and red blood cells.

The lumbar marrow showed a moderate erythroblastic and lymphocytic hyperplasia. There were also many megakaryocytes, stem cells and plasma cells; myelocytes occurred in moderate numbers but adult polymorphonuclear leukocytic cells were quite scanty. The sternal and femoral marrows appeared similar though not quite as active.

The pathological diagnoses were: bilateral organizing pneumonia, bilateral serofibrinous pleuritis, hepatomegaly, splenomegaly, enlargement of mesenteric and tracheal lymph nodes, hypertrophic arthritis, diverticulitis and diverticulosis of colon, hyperplasia of bone marrow with maturation arrest of the neutrophilic series (dysoremos neutrophilia).

Cultures of the heart's blood and spleen showed no growth while those of the lungs showed *Streptococcus viridans*.

Analysis of Case Reports

As the clinical and pathological features of the above case conform rather closely to the nine previously reported cases they will all be discussed together.

All cases have been in individuals between 45 to 65 years, equally distributed between the sexes. The cases have been widely scattered geographically. The occurrence of a marked loss of weight, six to 65 pounds has been usual, with an average loss of about 40 pounds. Intermittent periods of moderate fever have been noted, rarely going above 101° F. The arthritis is invariably of a chronic type—only one case had less than two years' duration—showing repeated acute migratory exacerbations, characterized by pain, tenderness, limitation of motion, and less often by local heat and redness. The ankles, wrists or knees frequently are the first joints involved, but before this acute manifestation has subsided, the shoulders, elbows, interphalangeal and other joints are involved in rapid succession. After the acute phase, stiffness and slight limitation of motion not infrequently exist. Roentgenologically, the changes in the articular cartilages

and in the bones have not been marked. Six cases showed changes suggestive of infectious arthritis, and three showed only minor indeterminate changes. One case showed complete ankylosis of some of the joints.

A firm, smooth, non-tender, persistently enlarged spleen has been noted in all cases, the inferior edge having been palpated at various points between the left costal margin and the level of the umbilicus. The enlargement is usually quite definite and the spleen extended to the umbilicus in four cases. Very little variation in size has been noted in the different cases upon repeated periodic examinations. Four spleens have been studied pathologically, two as surgical specimens and two as necropsy specimens. In three cases there was found dilatation of the sinuses, thickening of intersinusoidal spaces, enlarged Malpighian corpuscles with prominent germinal centers, and many plasma cells diffusely distributed. In two cases there were a few phagocytosed red blood cells. In the case of Craven and in that of Price and Schoenfeld there was noted an increase in eosinophiles. In the case here reported the splenic corpuscles were not large and the sinuses inconspicuous. There were many plasma cells, rare stem cells, occasional phagocytosed red blood cells, a few nucleated red blood cells, and relatively few polymorphonuclear leukocytes.

In only two cases was the liver palpable clinically. In the two cases operated upon the liver was found moderately enlarged, and the livers examined in the two necropsy cases weighed 2100 and 2000 grams, respectively. Sections of liver in three cases examined showed nothing remarkable.

In six cases there was noted pigmentation of the skin, confined chiefly to exposed surfaces.

In five cases, there was more or less slight general lymph node enlargement. Price and Schoenfeld noted "myeloid changes" in the material they examined. In my case, sections of tracheal and mesenteric nodes showed an obliteration of the normal architecture by the diffuse infiltration with plasma cells, a few stem cells, rare myelocytes, and an occasional phagocytosed lymphocyte and red blood cell.

All cases upon admission have shown a total white count varying from 800 to 4,200 with an average of about 2500. The admission differential showed the adult polymorphonuclear leukocytes varying from 14 to 79 per cent with an average of about 50 per cent; eosinophiles 1 to 12 per cent, 4 cases showing an eosinophilia at some time during the course of the disease; lymphocytes 14 to 86 per cent with an average of about 40 per cent. There was no mention of young cells of the granulocytic series, except in Price and Schoenfeld's case, where 3 per cent of myelocytes were found on one occasion, and 2 per cent another time. On one examination 20 per cent stabs were found. In my case, myelocytes were frequently found, on one occasion to the extent of 9 per cent. Young polymorphonuclear leukocytes were frequently found to exceed 30 per cent. In most cases there was a great variation in the proportion of adult polymorphonuclear leukocytes from time to time.

The red blood cell count varied from 3,000,000 to 4,800,000, and in all cases where many counts were performed, at some time in the course of the disease there was a drop below 3,500,000. The hemoglobin changes corresponded fairly closely with those of the red blood cells. The morphological characteristics of

the red blood cells showed few changes. The platelets have occurred in normal numbers. The bleeding time and clotting time have been found essentially normal.

Bone marrow studies have been made only in the two necropsy cases. Price and Schoenfeld found the sternal marrow to show "hyperplasia of marrow for patient's age with few bone marrow giant cells. Active myelosis throughout." The lumbar marrow in my case showed a moderate number of megakaryocytes, plasma cells and stem cells. The most notable feature was a partial maturation arrest of the neutrophilic series (dysoremos neutrophilia), there being a moderate number of the younger cells, but adult polymorphonuclear leukocytes being rare. The sternal and femoral marrows were similar though less active.

Examination of the vertebral column in my case showed nothing more than the changes of hypertrophic arthritis. Price and Schoenfeld found the knee joint, in their case, to show active chronic inflammation of the periarticular tissue and a marked infiltration of the adjoining periosteum with lymphocytes and plasma cells.

Urobilin was found in the urine in four cases. In several cases the urine was not tested for this.

Two cases in which glucose tolerance tests were performed showed a decreased tolerance.

Bacteriological studies have been negative.

Comment

The etiology of this disease remains to be proved. No explanations beyond those suggested by Felty have been advanced; namely, that there is one pathological process, caused by a noxa, which concomitantly affects the spleen, blood and joints; or that the arthritis is a process different from the remainder of the picture.

That there may be a blood dyscrasia is worthy of consideration, though further study is necessary to establish this as a fact. In Alessandrini's case what was thought to be a large spleen was found four years before the symptoms of arthritis began. In the other cases the relation is not known. Although the joint symptoms dated back for some time, the size and character of the spleens indicate that they had been enlarged for some time. In my case, the joint symptoms began only 10 days before admission, whereas the spleen was found two cm. below the costal margin, and in view of its pathological characteristics and the fact that it stayed at the same level, there is reason to believe that it may have been enlarged for some time.

The fact that soon after the splenectomy in Hanrahan and Miller's case there was a definite improvement of the arthritic symptoms, objectively as well as subjectively, within five weeks, and the fact that within four months the red and white counts were normal, suggest that the two processes are related and that a hematological basis may be the underlying cause. After splenectomy in Craven's case there was similar improvement, though not as marked. However, both from an etiological and therapeutic point of view it would be interesting to know the present status of these two patients, as not infrequently in other blood dyscrasias the improvement following splenectomy is only transitory.

In my case, a few stem cells and nucleated red blood cells were noted in the spleen, whereas adult neutrophiles were relatively rare. In the lymph nodes were seen a few stem cells and myelocytes. The most significant hemopoietic changes were found in the bone marrow, which showed a hyperplasia of all series, and although many stem cells and myelocytes were seen, adult polymorphonuclear leukocytes appeared rather rare, there apparently being some inhibiting factor preventing many of these granular cells from reaching maturity. This condition of the marrow, though not as marked, is analogous to that seen in cases of agranulocytosis showing maturation arrest as described by Fitz-Hugh and Krumbhaar [6] and later by Jackson and Parker.[7] This inability of the bone marrow to generate many mature neutrophiles was further manifested in my case at the time when with a severely ulcerated and sore throat, and later with a pneumonia, there was no increase in the polymorphonuclear leukocytes. There was a similar failure of response in Price and Schoenfeld's case during an attack of acute fibrinous pericarditis, and in all the other cases during the periods of acute exacerbation of the joint symptoms. Furthermore, if the bone marrow could generate polymorphonuclear neutrophiles in a normal manner, the pneumonic lung in my case should have contained more polymorphonuclear leukocytes, whereas those present no more than equalled the number of lymphocytes and plasma cells. One would also expect the fibrinous pericarditis of Price and Schoenfeld's case to show a reaction consisting chiefly of polymorphonuclear leukocytes, but they describe the cellular reaction as consisting chiefly of lymphocytes, plasma cells and eosinophiles. Additional evidence of a blood dyscrasia is the fact that with nucleotide treatment for several weeks there was no appreciable change in the white blood cell count in my case.

The number of adult polymorphonuclear leukocytes in the blood has sometimes been 20 per cent or less, and the bone marrow apparently attempts to compensate by sending out the younger forms into the peripheral blood.

With such lowering of so highly a potent barrier to infection, it is easy to see how noxious agents may gain a foothold, either through allergic mechanisms or by actual bacterial invasion, and produce the inflammatory changes noted in these cases. Just as in agranulocytosis there is a predilection for infections of the throat, so in these cases there is a predilection for the joints. Yet either may show manifestations elsewhere, such as acute fibrinous pericarditis, and pneumonia. One would expect to find associated inflammatory conditions more frequently if carefully sought for.

If one assumed allergy to play a rôle, it would be easy to explain the eosinophilia, the plasma cell and eosinophile infiltration in some of the organs and the rapid onset and disappearance of the acute arthritis without many sequelae. However, such an assumption is mere speculation.

Though agranulocytosis and Felty's syndrome seem to have many features in common, they are entirely separate entities. The former usually has a more sudden onset, is rapidly fatal if not treated, has a predilection for females, is very frequently associated with angina, and rarely has as high a white count. Of 103 cases analyzed by Jackson and Parker, 58 had white counts less than 1000 and only seven had a count of more than 2000. Moreover in agranulocytosis there is a more marked neutropenia, eosinophiles are quite rare or absent, the spleen is rarely obviously enlarged and never greatly so, and the bone marrow shows but few if any adult neutrophiles.

Still's [8] disease is similar in that there is a chronic arthritis, splenomegaly, enlargement of the lymph nodes, fever, emaciation, occasional eosinophilia, secondary anemia and rarely subcutaneous nodules. It is different in that it occurs in children, usually has a leukocytosis rather than marked granulopenia and neutropenia, and is characterized by a more crippling form of arthritis.

Many of the features of these cases are similar to those of other forms of chronic rheumatoid arthritis. Of 250 cases of chronic arthritis studied by Eaton [9] there were only three cases with a normal blood picture. The hemoglobin was below 75 per cent in 68.8 per cent of the cases and below 60 per cent in 15.2 per cent; the red blood cell count was below 4,000,000 in 10.4 per cent; the white blood cell count below 6000 in 22 per cent; the polymorphonuclear leukocytes under 60 per cent in 43.2 per cent; the lymphocytes over 35 per cent in 47.2 per cent. A marked shift to the left occurred in 37.2 per cent, with 2 to 15 per cent juvenile polymorphonuclear leukocytes in 44 per cent, and 5 per cent or more eosinophiles in 9.2 per cent. Pemberton and McRae each analyzed a large series of cases and, though differing to some degree in the figures, found essentially the same general changes. Slight enlargement of the spleen and eosinophilia associated with chronic arthritis have been frequently described. However, in no case have I been able to find such persistently marked leukopenia or granulopenia (adult polymorphonuclear leukocytes sometimes being less than 10 per cent). Nor has there been such failure of response of the white count in the presence of swollen, hot, painful joints or such acute infections as fibrinous pericarditis (Price and Schoenfeld), angina and pneumonia.

Summary

1. The cases of Felty's syndrome which have been reported have shown it to be a disease of middle-aged individuals characterized by migratory, polycyclic chronic arthritis, splenomegaly, marked leukopenia, marked granulopenia, distinct loss in weight, slight secondary anemia and intermittent fever. Less often there have been noted enlargement of lymph nodes, pigmentation of the skin, urobilinuria, enlargement of the liver and eosinophilia. Two cases have been treated with some improvement by splenectomy.

2. A case of this disease with autopsy is reported.

3. An attempt has been made to explain the primary disturbance as a blood dyscrasia in which there is an arrest in the maturation of the polymorphonuclear leukocytes (dysoremos neutrophilia).

REFERENCES

1. Felty, A. R.: Chronic arthritis in the adult, associated with splenomegaly and leukopenia, Bull. Johns Hopkins Hosp., 1924, xxxv, 16.
2. Hanrahan, E. M., and Miller, S. R.: Effect of splenectomy in Felty's syndrome, Jr. Am. Med. Assoc., 1932, xcix, 1247.
3. Craven, E. B.: Splenectomy in chronic arthritis, associated with splenomegaly and leukopenia (Felty's syndrome), Jr. Am. Med. Assoc., 1934, cii, 823.
4. Alessandrini, P.: Felty's syndrome, Minerva Med., 1934, i, 310.
5. Price, A. E., and Schoenfeld, J. B.: Felty's syndrome, report of a case with complete postmortem findings, Ann. Int. Med., 1934, vii, 1230.

6. Fitz-Hugh, T., Jr., and Krumbhaar, E. B.: Myeloid cell hyperplasia of the bone marrow in agranulocytic angina, Am. Jr. Med. Sci., 1932, clxxxiii, 104.
7. Jackson, H., Jr., and Parker, F., Jr.: Agranulocytosis, its etiology and treatment, N. E. Jr. Med., 1934, ccxii, 137.
8. Still, G. T.: On a form of chronic joint disease in children, Med.-Chir. Soc. Trans., London, 1897, lxxx, 47.
9. Eaton, E. R.: Chronic arthritis; a report based on the blood cell count in 250 cases, Jr. Am. Inst. Homeop., 1932, xxv, 125.

NEUROCIRCULATORY ASTHENIA: REPORT OF A CASE TREATED BY ADRENAL DENERVATION *

By John P. Anderson, M.D., F.A.C.P., *Cleveland, Ohio*

The term, neurocirculatory asthenia, is used to represent a syndrome characterized by a sense of fatigue, palpitation, precordial pain, and a tendency to giddiness. The symptom complex it presents is almost as definite as that of angina. It has been called by various other names, for example, irritable heart, effort syndrome, and disordered action of the heart, but none is quite so descriptive as neurocirculatory asthenia.

Persons afflicted with this condition are usually thin and asthenic in stature and appearance. They have quick, nervous temperaments and are intelligent. They have a marked degree of initiative but usually lack the physical stamina to carry on sustained activity without suffering undue fatigue. Whether this is essential to the syndrome or incidental is unknown. It would appear that they have been unable to train their involuntary nervous systems and still react to fear, joy, sorrow and other emotions as adolescents; but whether this is due to lack of effort on their part or to a hypersensitive involuntary nervous system is uncertain.

Dr. Crile has suggested that the condition of neurocirculatory asthenia is caused by excessive adrenal activity which produces increased drive on the whole involuntary nervous system. On this basis he has advocated adrenal denervation, and this report illustrates the beneficial effects of the operation in controlling the circulatory symptoms in a patient with neurocirculatory asthenia.

Case Report

A single girl, aged 21 years, who was employed as a secretary, first consulted Dr. Crile in 1921 for nervousness and enlargement of the neck. Her birth had been premature (at seven months) and difficulties had been encountered in maintaining her nutrition. She had always been considered as a delicate child. She had had diphtheria in childhood, and following this a tonsillectomy had been performed. The menses were regular and normal with no pain.

She stated that her neck had been slightly enlarged and that she had been a little nervous for several years, but that during the last year these symptoms had progressed. She also suffered from insomnia. She noticed palpitation and slight dyspnea with effort and also had difficulty in swallowing when she was nervous; she said she felt as if she had a lump in her throat. There had been no loss of weight. Her appetite was good and she had had few digestive upsets. The bowels were regular,

* Received for publication January 2, 1935.

and there was no bladder frequency or nocturia. She had very few colds, but complained that she tired very easily.

On examination, she was 5 feet, 7 inches tall and weighed 130 pounds. There was a slight symmetrical thyroid enlargement with increased pulsation of the superior thyroid vessels. The heart was not enlarged. The pulse rate was 120. The diagnosis was mild hyperthyroidism, and an operation was performed at which 40 grams of thyroid tissue were removed. This the pathologist reported as colloid goiter with no hyperplasia.

In 1923, the patient reported that she still fatigued easily, was less nervous, but still had palpitation. Her weight had not changed. It was thought that she probably had recurrent hyperthyroidism and sedatives were prescribed.

From 1923 to 1930 she worked steadily as a stenographer and secretary for a busy executive. She was annoyed by palpitation and fatigued easily. She was full of ambition but lacked the physical ability to accomplish what she wished without undue fatigue, and she had to force herself to get through her work.

I first saw her in June 1930, when she consulted me for an examination of her heart condition. This was prompted by the fact that she had twice been refused life insurance and had been unable to obtain permission to swim in a Y. W. C. A. pool, because of a rapid heart rate. At that time, she still weighed 130 pounds. The temperature was 98.6° F., the pulse rate 126, and the blood pressure 138 systolic, 70 diastolic. She had no exophthalmos and no lid lag, and there was no palpable thyroid tissue, but she displayed some digital tremor and seemed nervous. Her extremities were clammy. The heart was not enlarged. The sounds were clear and without any murmurs. There were no signs of congestive failure in the lungs, liver or extremities and no cyanosis of the extremities.

My first impression was that she had recurrent hyperthyroidism but the basal metabolic rate was — 11 per cent, which immediately raised the question of neurocirculatory asthenia. Lugol's solution was administered daily for one month. The patient was still nervous and irritable and the pulse rate varied between 100 and 120. There was still some digital tremor. The Lugol's solution was continued for another month. She then had no digital tremor, the basal metabolic rate was — 7 per cent and the pulse rate 88.

In October 1930, she had been working hard and was excessively stimulated. She was troubled with insomnia, her hands were cold and clammy, the pulse rate was 150 and the blood pressure 130 systolic, 70 diastolic. The administration of Lugol's solution was renewed daily, and a month later the pulse varied from 96 to 108, and she had a marked sinus arrhythmia. An electrocardiogram showed nothing abnormal aside from the sinus arrhythmia. The Lugol's solution was discontinued and a month later the pulse was 130.

Her condition remained unchanged for four months until April 1931. At that time she was working very hard and felt nervous, and her ankles were swollen. Digitalis was prescribed (1 grain three times daily). This induced nausea on the eighth day but the edema had disappeared. The pulse rate was 100. The digitalis was continued, but even very small doses induced nausea and she refused to take any more. In July 1931, ammonium chloride and salyrgan were started and were continued on an average of once a week for six weeks. The pulse rate averaged 130 each time she was observed, but the salyrgan controlled the edema of the legs. There were never any pulmonary congestive râles or tenderness of the liver.

In November 1931, she made a trip to California and had no trouble on the way. Her nervousness subsided while she was away. In December 1931, her ankles were still slightly swollen and her extremities were cold, clammy and mottled.

In July 1932, her chief complaint was easy fatigability and aches at the back of the neck. She said that she had noticed the cold a great deal during the past winter and always required about twice as many bed clothes as other persons. She had

recognized no edema during the last year. Her heart continued to thump at the slightest provocation and her extremities continued to sweat easily. She had used no medicine.

At examination on July 16, 1932, that is, two years after my first examination, the temperature was 99°, the pulse rate 126 and the blood pressure 130 systolic, 80 diastolic. The hands were warm and clammy. She displayed no cyanosis, no thyroid or lymph glandular enlargement, and the lungs were clear. The heart borders were 3 and 10.5 cm., the sounds were regular with a systolic murmur at the apex. The remainder of the examination, including a blood count and urinalysis, was normal. An electrocardiogram showed normal rhythm and conduction with inverted T_3. Vagal pressure, eye ball pressure, or bending over and compressing the abdomen caused no appreciable change in the pulse rate, but lying down reduced it from 126 to 108.

She received Lugol's solution (8 minims twice daily) for two weeks, but this produced no change in her condition. The pulse rate when standing was 120; when lying down, 72 to 88; after touching toes 15 times, 132; after lying down it reached 72 with marked sinus variation. Deep inspiration caused marked slowing of the pulse with sinus arrhythmia, whereas before she had taken the Lugol's solution, this had produced no change.

After consultation with Dr. Crile, she was advised to have an adrenal denervation and she entered the Cleveland Clinic Hospital in September 1932, with symptoms of tremor, cold hands, palpitation, tachycardia (pulse rate 130), nervous excitability and fatigability, and flushing of the neck and chest. The basal metabolic rate was −8 per cent.

Dr. Crile performed a left adrenal denervation on September 28, 1932, and right denervation on October 11, 1932. She was in the hospital 23 days. On discharge, her hands were warm and dry and she had no tremor. She was sleeping well and could relax easily without any sense of inward nervousness and had no palpitation or precordial distress. The pulse rate was 80. One month later she was feeling well and the pulse rate was 74. The extremities were dry and warm, she had no palpitation and the flushing of the neck had disappeared.

For one year she lost an average of two pounds each month. In February 1933, her menses became irregular. One period interval would be four weeks and the next two weeks. Examination showed that the right ovary was about twice the normal size and the presence of a retention cyst was suspected. Six injections of antuitrin S were administered and the menses became regular.

During the hot weather that summer there was some aching under the left scapula but the patient had no palpitation or edema. The pulse rate remained between 72 and 78. The menses became irregular again in August 1933. Antuitrin S seemed to help regulate them, but when larger and larger doses were required, its use was abandoned.

The patient then had irregular menses with periods of amenorrhea for two to four months. In September 1933, one year after the operations, her weight had fallen from 129 to 100 pounds, and she then complained of marked urinary frequency and urgency. The urine was examined and showed no pus or casts but 1 + albumin; the specific gravity was 1.033. Another specimen was collected in the early morning and showed no albumin which indicated that the albuminuria might be postural. A 24 hour output was then recorded and it was over 4 liters, of which the night specimen was 1125 c.c.

Several doses of pitressin were given hypodermically and the 24 hour urinary output was recorded afterwards. These were 3000, 2000 and 1500 c.c. respectively. There was no further loss of weight after these injections, and three months later she had gained five pounds. Although the pulse rate and blood pressure did not change, the injections of pituitary extract always caused a little shock and nausea and the

patient preferred not to continue them. Whole pituitary substance was given in doses of 5 grains daily, but caused very little effect, so it was discarded.

To date, September 1934, her condition continues about the same. She has gained no more weight. There is still an excessive urinary flow with much urgency at times. The menstrual periods are irregular. An osteoma developed along the crest of the left ilium which was a little tender to pressure. The blood calcium is 10.78 mg. per cent. The heart has remained entirely stable. The pulse rate has never been above 90 since the denervation of the adrenal glands, and the rate is usually 72 to 78. The systolic murmur at the apex is now barely audible. There has never been any recurrence of the sense of palpitation, flushing, inward nervousness or cold extremities, and there has been no undue fatigability in spite of the loss of weight. The patient herself is most enthusiastic about the results of the operation.

Comment

In my experience, neurocirculatory asthenia has been rather difficult to control with medical measures. Digitalis has little or no effect in slowing the heart rate and no effect on the other symptoms. Sedatives such as bromides and barbiturates have little effect, and drugs which act on the sympathetic nervous system, such as quinine and ergotin and ergotamine, have been of but questionable value. In fact, the only thing that has really helped has been about one or two years of intensive rest and convalescent treatment, and that is a form of therapy that is seldom practicable. The fact that a thyroidectomy was performed on this patient in 1921 and failed to cure her symptoms indicates once again that the symptoms of neurocirculatory asthenia are not relieved by thyroidectomy.

It is very gratifying in this case to find a complete cure of all the symptoms of neurocirculatory asthenia by the adrenal denervation, although there is evidence of a disturbance of the pituitary gland following the operation. The fact that there was an increased urinary output with a negative water balance which appeared after the operation along with irregular menses and later amenorrhea when both of these factors had been very stable prior to the operation is presumptive evidence, at least, of some hypofunction of both the anterior and posterior lobes of the pituitary gland.

But despite these complications, the patient's condition has been very much better generally, and the abnormality of the circulation has been entirely controlled since the operation.

PAROXYSMAL VENTRICULAR TACHYCARDIA; REPORT OF A CASE ILLUSTRATING ALL THE ACCEPTED DIAGNOSTIC CRITERIA *

By Aaron E. Parsonnet, M.D., C.M., F.A.C.P., *Newark, New Jersey*

Although there is a growing tendency among recent authors to minimize the rarity of paroxysmal ventricular tachycardia, nevertheless, when all the accepted criteria warranting such a diagnosis are made requisite, this type of abnormal cardiac rhythm looms rarer than ever.

The literature, starting with the work of Lewis,[1] has been materially enriched by contributions devoted to the study of paroxysmal tachycardias, some of which

* Received for publication September 10, 1935.

are unquestionably of the ventricular type. However, after careful scrutiny of the available material, a large percentage of the reported cases falls by the wayside as either unproved, doubtful as to point of origin, or totally worthless for statistical data because of lack of electrocardiographic corroboration. In two exhaustive studies made by Gilchrist [2] and Strauss,[3] the former accepts practi-

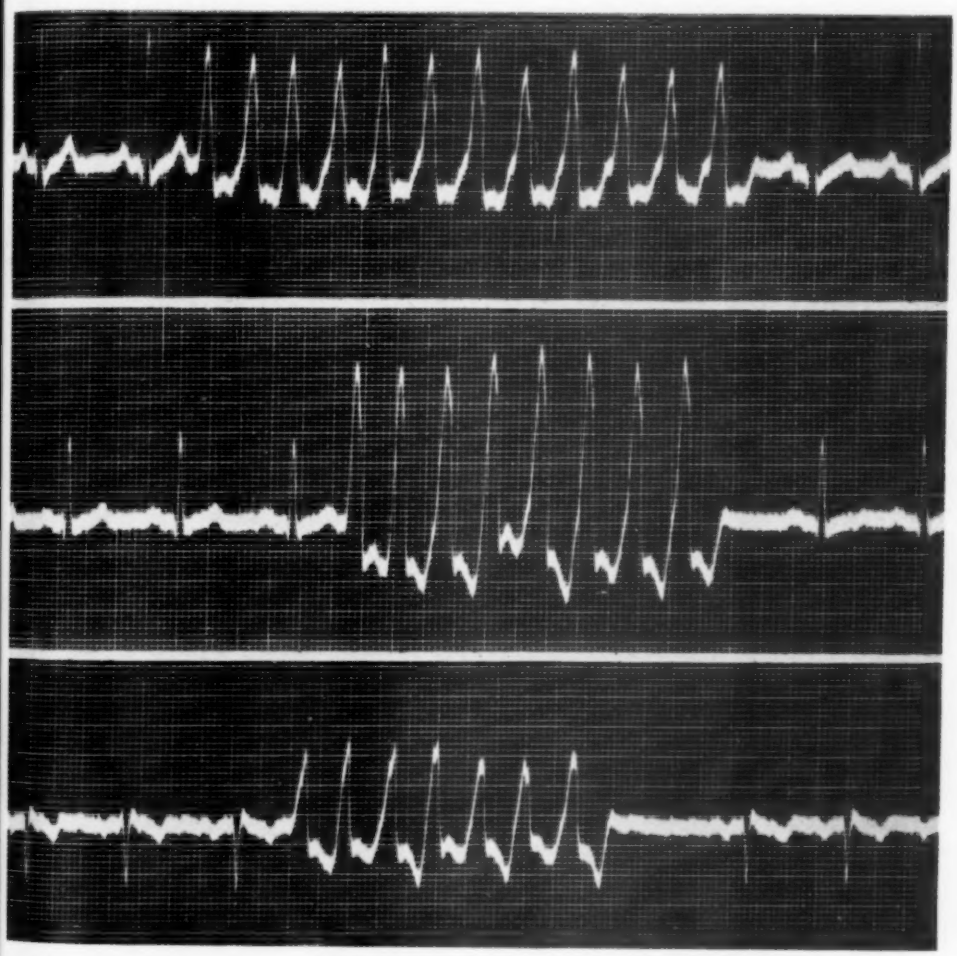

FIG. 1. Tracing taken on May 10, 1932, showing the typical paroxysms of ventricular tachycardia. The variations in the length of the interventricular intervals may be distinctly observed.

cally all reported cases as true ventricular paroxysms, while the latter, on the other hand, disposes of the majority of the 65 instances recorded up to 1930, as distinctly doubtful. There is a definite reason for such marked diversity of opinion among careful investigators: electrocardiographic methods of examination are still quite recent and poor tracings and standardizations were the rule up to but a very few years ago. With the practically perfect modern instruments and, of still greater importance, the improved technic and resultant rapid handling

of suspected patients, a paroxysm will rarely escape the observer and a good permanent record will be secured.

The criteria warranting the diagnosis of paroxysmal ventricular tachycardia as outlined by Robinson and Herrmann,[4] must be fully met and are as follows:

1. The electrocardiographic tracings must definitely establish the fact that the cardiac impulses responsible for the rapid ventricular rate are of distinct ventricular origin.

2. The ventricular complexes must be both preceded and followed by auricular complexes of slower rate.

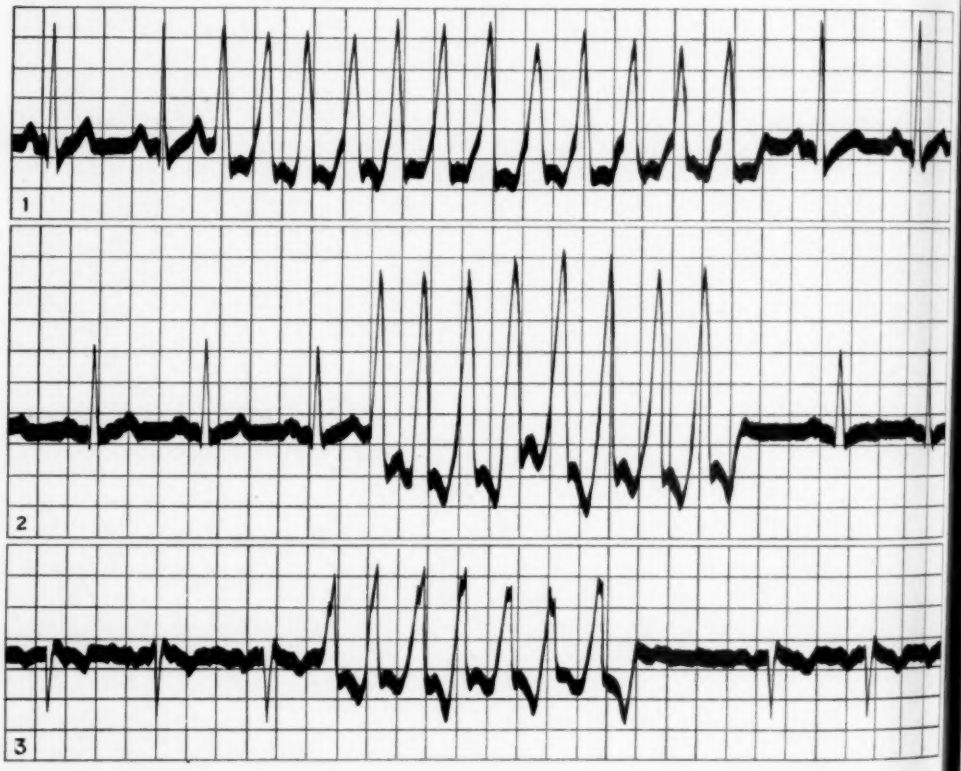

FIG. 2. Schematic representation of the above tracing to more clearly note the characteristics of the paroxysms.

3. The ventricular complexes must be abnormal in form and, should there be any isolated extrasystoles preceding or following the paroxysm, these must resemble in type the ones seen during the attack of tachycardia.

In this connection, Robinson and Herrmann [4] point out that the abnormal ventricular complexes alone cannot serve as proof of ventricular origin, for their bizarre form may be produced by intraventricular conduction disturbances. If, however, at the termination of the paroxysm no such disturbed conduction is exhibited, the unusual form of the complexes will serve further to substantiate their ventricular origin. Robinson [5] also brought out the fact that, when the cardiac rate is very fast, conduction disturbances may often be overlooked. The

diagnosis of paroxysmal ventricular tachycardia can be made still more certain when, as Strong and Levine [6] pointed out, the rapid succession of ventricular complexes discloses a slight but nevertheless a definite irregularity of time spacing not met with in any of the other forms of paroxysmal tachycardia.

It would be useless repetition and distinctly burdensome to give a detailed review of the literature; this has been very ably done by Strauss.[3] It is interesting to note, however, that as late as 1921, the entire number of published cases comprised 16, of which only six could be considered authentic. The writer's experience has been similar for, although over 90 cases were carefully examined in the available literature, the data in a large percentage were found unconvincing.

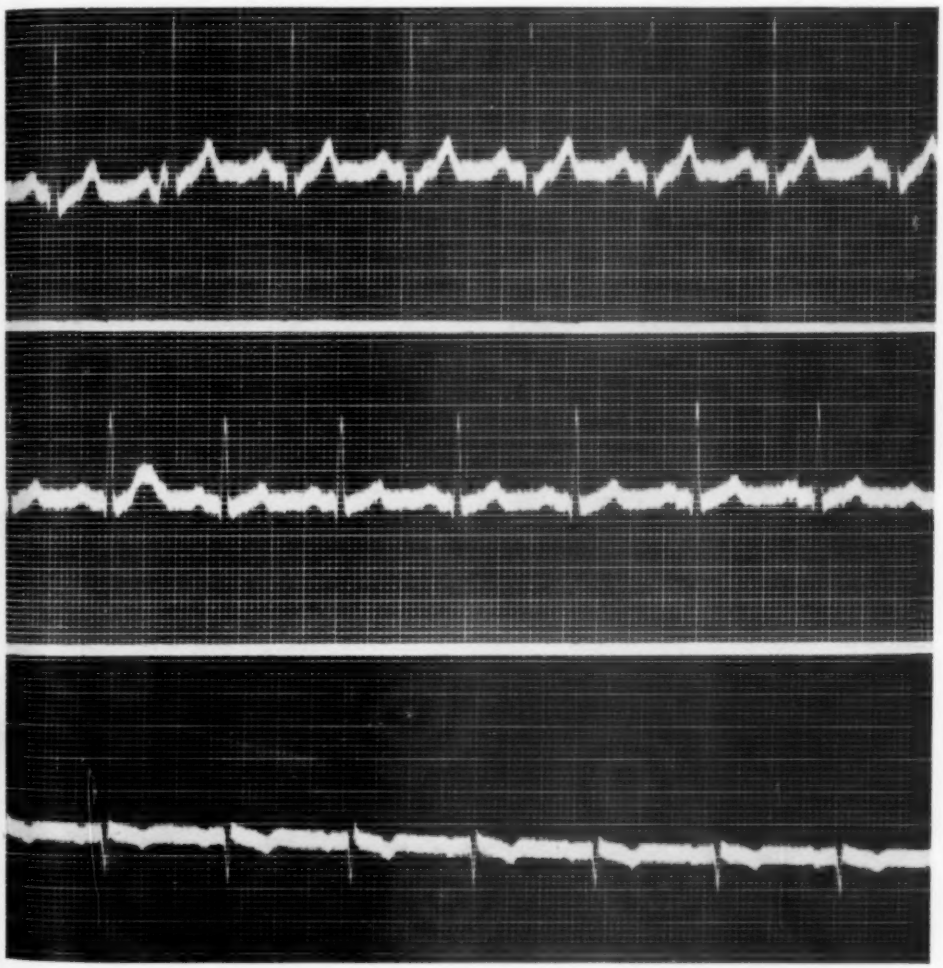

FIG. 3. Electrocardiogram obtained before the onset of the paroxysm.

It is not amiss, therefore, to present the following case of paroxysmal ventricular tachycardia exhibiting all the essential electrocardiographic features of this still rather rare arrhythmia.

CASE REPORT

History. F. C., male, aged 63, a native of the United States, receiving clerk by occupation, was seen in consultation on May 10, 1932. His chief complaints at the time were: dyspnea upon exertion, precordial discomfort and occasional attacks of palpitation. His family history was unimportant, his parents having died of old age and one brother and two sisters during infancy. His previous history was un-

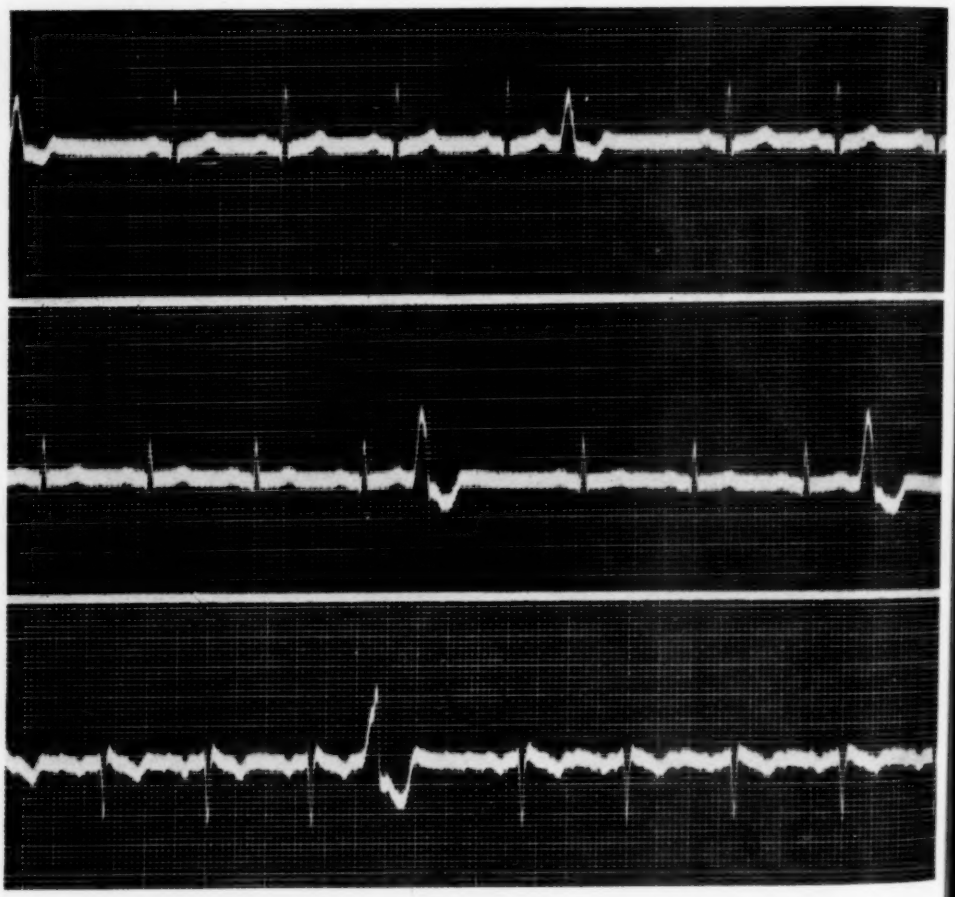

FIG. 4. Electrocardiogram taken after the paroxysm subsided. Note the isolated extrasystoles in each lead and compare their form with those in figure 5.

eventful, except for the usual diseases of childhood and a minor surgical operation for ischiorectal abscess at twenty-five. He had been married 35 years, and had six children all living and well. His wife always enjoyed good health and gave no history of miscarriages or stillbirths. He was always temperate in his habits, using no tobacco or alcohol and drinking tea and coffee moderately. His exercise consisted chiefly in walking to and from work. He always enjoyed a good appetite, was a hearty eater, but habitually was a very poor sleeper.

Present Illness. Although dyspnea and palpitation were symptoms familiar to him for the last year or two, he was quite sure that these were very much aggravated

since the beginning of April 1931, when in the course of his work he met with an accident. A heavy bale of wrapping paper struck him, knocking him down and fracturing his right clavicle and arm; he also received a crushing blow over the left chest, but no ribs were broken. Following this occurrence he became very short of breath even upon the slightest exertion, and the dyspnea would invariably be accom-

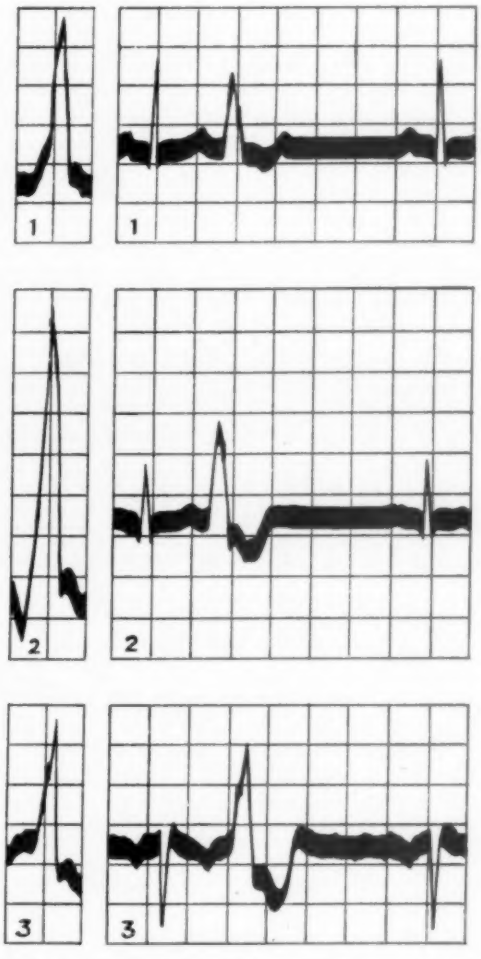

FIG. 5. Redrawn section of the electrocardiogram (figure 1), isolating one ventricular complex from each lead and comparing it with the corresponding ectopic beat in figure 4. Note the striking structural similarity.

panied by marked precordial pain and palpitation. At times, while walking, he would stop short, being conscious of a sudden beginning and termination of rapid heart action.

Physical Examination. The patient was 5 feet, 7 inches tall, and weighed 170 pounds. He appeared chronically ill, very dyspneic, and slow and deliberate in his movements. His skin was free from eruptions, dry, and had a leathery feel; his lips and nail-beds were moderately cyanosed. Oral examination showed moderate dental sepsis, with many teeth missing; the tongue was thickly coated. The naso-

pharynx was normal. The sinuses transilluminated well and the larynx was freely movable. There was no thyroid enlargement. The eyes reacted to light and to accommodation; the pupils were regular, both palpebral fissures equal. The conjunctivae were clear. A well-marked arcus senilis was present. The ophthalmoscopic examination revealed increased tortuosity of the retinal vessels.

The chest was well formed and disclosed no abnormal prominences or depressions, but scattered moist râles were heard posteriorly in both bases.

The heart was enormously enlarged to percussion in all its diameters and the aorta markedly widened. The heart sounds were muffled and toneless, and the regular rhythm was frequently interrupted by extrasystoles, isolated and in showers. These were detected with difficulty at the radial artery. There was a marked pulse deficit. Under a moderate spirometric exercise test the patient became cyanotic and very dyspneic, showing a very poor myocardial reserve. An occasional systolic blow was heard at the apex which was also elicited over the aortic area. Repeated blood pressure readings averaged 140 systolic and 40 diastolic.

The abdomen was prominent; no masses and no ascites were noted. The liver was enlarged and tender to pressure, the lower margin extending four fingers below the costal margin. The spleen was not palpable.

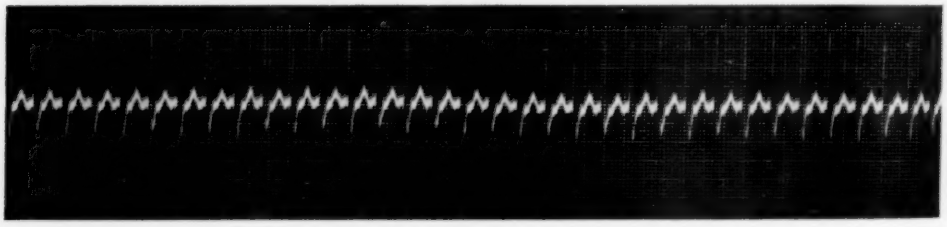

FIG. 6. A tracing of a typical paroxysmal auricular tachycardia inserted for comparison. Note the practically clock-like regularity of the interventricular time intervals here as compared with the variations in the interventricular intervals as seen in figure 1.

The genito-urinary tract, with the exception of a moderately enlarged prostate, disclosed no abnormalities.

Fluoroscopic examination revealed a markedly enlarged cardiac shadow, aortic in configuration, a very much widened aorta and an accentuated aortic knob. The transverse diameter of the chest measured 29.7 cm., with a maximum transverse cardiac diameter of 18.8 cm. The lung fields were clear. The diaphragmatic excursions were limited.

Laboratory Data. The urine showed a 1 plus albumin test, a few small granular casts and an occasional pus cell; many cylindroids were noted. The blood count showed a hemoglobin of 82 per cent with 4,400,000 red blood cells, and 9,600 white blood cells. The differential count showed 59 polymorphonuclears, 37 lymphocytes and 4 eosinophiles. The blood chemical tests showed a urea nitrogen of 16.8, creatinine 1.5, and sugar, 95 mg. per hundred cubic centimeters. The Wassermann and Kahn tests were negative.

The electrocardiograms taken on May 10, 1932 (figures 1 and 2) showed the following: There were no gross errors of conduction. The P–R intervals were 0.20 sec.; the QRS complexes were upright and of high voltage in Leads I and II, and inverted in Lead III showing a left axial rotation. The T-waves were dominantly upright in Leads I and II, and inverted in Lead III. They exhibited a low take-off in Lead I. The P-waves were upright in Leads I and II, and inverted in Lead III. The dominant rhythm is interrupted in every lead by showers of ventricular extrasystoles reaching a rate of 210 beats per minute. All the ectopic beats originate from

a single ventricular focus of irritability (figures 4 and 5). The auriculoventricular rate before the onset of the paroxysm is 90 beats per minute. (Figure 3.)

The patient is now 66 years old and has had several severe attacks of coronary occlusion; the paroxysms of ventricular tachycardia still continue at irregular intervals.

Summary

A case of undoubted paroxysmal ventricular tachycardia is reported in which all the essential criteria warranting such a diagnosis are exhibited. An exhaustive review of most of the available literature established the rarity of cases of this condition properly authenticated by satisfactory electrocardiographic proof. Such proof, however, is here presented as unmistakable evidence for the above diagnosis.

BIBLIOGRAPHY

1. Lewis, T.: Paroxysmal tachycardia, Heart, 1909–1910, i, 43.
2. Gilchrist, A. R.: Paroxysmal ventricular tachycardia, Am. Heart Jr., 1926, i, 546.
3. Strauss, M. B.: Paroxysmal ventricular tachycardia, Am. Jr. Med. Sci., 1930, clxxix, 337.
4. Robinson, G. C., and Herrmann, G. R.: Paroxysmal tachycardia of ventricular origin and its relation to coronary occlusion, Heart, 1921, viii, 59.
5. Robinson, G. C.: The relation of changes in the form of the ventricular complex of the electrocardiogram to functional changes in the heart, Arch. Int. Med., 1916, xviii, 830.
6. Strong, G. F., and Levine, S. A.: Irregularity of ventricular rate in paroxysmal ventricular tachycardia, Heart, 1923, x, 125.

EDITORIALS

THE DETROIT AND ANN ARBOR SESSIONS

THE return of the College, after ten years, to the city of Detroit gave to many of the older members an opportunity both to evaluate the progress of the College in this period of time and to appreciate the many alterations and advances in the medical institutions of Detroit and Ann Arbor. Changes have taken place; a normal healthy development has occurred. The College brought to this meeting a larger group of men better able to enjoy the richer intellectual fare provided for them.

In the minds of all was the memory of the man to whom the College owes so much, Dr. Charles G. Jennings. Both in the development of the policies of the general body of the College and in arousing the interest of the medical men of Michigan in the value of the College, Dr. Jennings played an important part. He it was who transmitted to the Regents the invitations to the College from the Medical Schools, the Hospitals and the Medical Societies of Detroit and Ann Arbor, to hold the Sessions of 1936 in Michigan. The acceptance was based in no small part upon his agreement to act as General Chairman. The success of this meeting constitutes a tribute to him since much of the labor was his and since those who took up the burden when he dropped it were his friends and carried out the work in the spirit of his wishes.

Perhaps at no meeting has there been more satisfaction among the Fellows both with the high quality of the General Sessions and with the interest and variety of the program of clinical meetings. The gratitude of the College is due to all who took part in the laborious task of arranging this highly successful meeting.

PNEUMOCOCCUS TYPE III PNEUMONIA

THE differentiation of the pneumococci into biological types led naturally to the hope that more intensive study of the clinical aspects of lobar pneumonia would disclose characteristic features which would be distinctive for the pneumonia caused by each type of the pneumococcus. This hope has as yet been only partially fulfilled, but a recent study by Cecil, Plummer and McCall [1] of 500 cases of Type III pneumonia adds further data in confirmation of earlier work that established important clinical facts bearing on infection with this organism.

The analysis of the incidence of Type III infections has shown again that though in the total of all pneumococcus pneumonias only about one in eight is due to Type III infection, in pneumonias occurring after 60 years of age Type III pneumococci are the commonest etiologic agent. In this age group the authors found in their recent study 32.8 per cent of Type III

[1] CECIL, R. L., PLUMMER, N., and MCCALL, M.: Pneumococcus Type III pneumonia, Am. Jr. Med. Sci., 1936, cxcl, 305–319.

infections. In all cases over 50 years the incidence of Type III infections was 24.2 per cent; while in cases under 50 years it was only 9.4 per cent. Since these figures accord well with those found in earlier series published by Cecil, Baldwin and Larsen [2] and by Blake [3] it may be considered clearly demonstrated that Type III pneumonia is a relatively rare variety before 50 but becomes the commonest type in the elderly.

The death rate in the 500 cases of Type III pneumonia analyzed was 42.2 per cent. This is in very close agreement with the figures derived from other large series. It seems, however, that this high death rate is not necessarily due entirely to the excessive virulence of the organism. The death rate of all types of pneumonia increases with each decade after maturity. Since Type III pneumonias are common among the aged, it is evident that a part of the high death rate may be due to the lessened resistance of those attacked. In the Bellevue series Cecil, Plummer and McCall have found that the death rate for Type III cases under 40 is not significantly higher than that of Type I or Type II. Approximately 40 per cent of all the Type III cases, however, were over 50 years of age, whereas only 18.4 per cent of the Type I cases were over 50 and only 31.7 per cent of the Type II cases. That the age incidence is, therefore, a factor in determining a part of the high mortality of Type III infections seems clear.

Another factor apparently is the tendency of Type III infections to attack those already debilitated by chronic disease. In the present series the incidence of systemic diseases, especially alcoholism and degenerative cardiovascular diseases, was 49.6 per cent. Blake found that even in the earlier age periods this same tendency could be observed. Comparable figures given for series of Type I and Type II cases show that systemic disease occurred in only 20.4 and 33 per cent respectively of these infections.

These considerations of the factors bearing on the virulence of the Type III pneumococcus seem of particular interest. The fact that this organism, unlike the Type I and II pneumococci, is not infrequently found as an apparently harmless saprophyte in the mouths of healthy individuals has always raised the question as to what determined its behavior in the cases in which it causes a highly fatal infection.

To this fundamental question no answer has been given, but when a more complete understanding is attained the explanation must include the behavior of this organism in relation to age and to chronic disease.

[2] CECIL, R. L., BALDWIN, H. S., and LARSEN, N. P.: Lobar pneumonia: a clinical and bacteriologic study of two thousand typed cases, Arch. Int. Med., 1927, xl, 253–281.

[3] BLAKE, F. G.: Observation on pneumococcus Type III pneumonia, Ann. Int. Med., 1931, v, 673–686.

BOOK REVIEWS

Laboratory Methods of the United States Army. Edited by MAJOR JAMES S. SIMMONS and MAJOR CLEON J. GENTZKOW (Associate editor). Fourth edition. Lea and Febiger, Philadelphia. 1935. 1091 pages. Price, $6.50.

This new edition of the Army Manual has been largely rewritten and considerably extended in scope. Twenty contributors are listed, chiefly members of the Medical Corps on the staff of the U. S. Army Medical School.

The book is primarily a laboratory manual. It covers in a severely practical way the usual field of medical bacteriology, serology, protozoölogy and clinical pathology, including quantitative chemical analyses of the blood and urine. There are also brief sections on mycology, on the helminths, and on the more important mosquitoes and other arthropod vectors, with tables and keys to facilitate identification. The individual parasites are not described, however. In addition there are sections on the filtrable viruses; chemical and bacteriological examination of water, milk, foods and beverages; toxicological procedures; autopsy technic and preparation of tissue sections; special methods applicable to veterinary medicine; and statistical methods.

The technic of the various laboratory examinations is given in detail, and the underlying principles are clearly explained, so that the procedures can be followed by technicians with limited experience. As a rule the authors have selected a single analytical method for each determination with occasionally an alternative procedure. In most instances the selections seem wisely made. Relatively less attention is paid to the clinical significance of the tests except in a few instances. Thus, tests of liver function and of kidney function are discussed at considerable length.

In general the subjects are adequately covered, and the work is reasonably well balanced. As is usually the case in books which are the product of a number of contributors, some subjects seem unduly stressed at the expense of others. The reviewer regrets, for example, that only 18 pages were allotted to hematology, less than half the space devoted to tests of liver function. He was also unable to find a description of the glucose tolerance test.

On the whole the book is well written and accurate and contains a great deal of carefully selected, useful information. It should be of great assistance to those who are engaged in the actual performance of these procedures. P. W. C.

The Practitioner's Library of Medicine and Surgery. Supervising Editor, GEORGE BLUMER, M.A. (Yale), M.D., F.A.C.P.; David P. Smith Clinical Professor of Medicine, Yale University School of Medicine; Consulting Physician to the New Haven Hospital. *Volume IX: Neurology and Psychiatry.* Associate Editors, JAMES C. FOX, JR., B.A., M.D., Associate Professor of Neurology, Yale University School of Medicine, and CLEMENTS C. FRY, B.S., M.D., Associate Professor of Psychiatry and Mental Hygiene, Yale University School of Medicine. xlviii + 1234 pages, 193 illustrations. D. Appleton-Century Company, Inc., New York. 1936. Price, $10.00 a volume.

In the preface to this ninth volume, *Neurology and Psychiatry*, of *The Practitioner's Library of Medicine and Surgery*, attention is very properly called to the fact that the ultimate welfare of the patient with a "nervous" disorder often depends upon the alertness and insight of the practitioner whom he first consults. To learn to appreciate the patient's personality make-up, and to recognize organic disease of the nervous system in its clinically incipient stage are the responsibilities of the physician toward this group of patients. Thirty-nine authors have contributed the forty-one chapters of this book. After sections in which the general principles of behavior, psychopathic personalities and their manifestations, and special methods of examina-

tion are considered, the individual affections of the nervous system are treated according to a grouping based upon etiological factors so far as is possible. This method brings together conditions in respect to which differential diagnosis is required and directs attention at once to such causal agencies as may be avoided or alleviated. Thus entire sections of from one to six chapters each are devoted to disease due to infection, to intoxication, to alimentary deficiency and to trauma.

It is quite impossible to attempt a critical evaluation of the individual sections of this book. In a general way it is evident that the editors have secured a degree of uniformity in style and a balance in treatment which is unusual in a work to which there have been so many contributors. Brief historical notes give added interest to many sections, and well chosen illustrations have been freely used. To those practitioners who think that neurology and psychiatry are abstruse specialties, of but little application in their daily routine, this volume can be enthusiastically recommended as readable, entertaining, informative and stimulating. It is a highly successful addition to *The Practitioner's Library*. C. V. W.

Essentials of Psychopathology. By GEORGE W. HENRY, M.D., Associate Professor of Psychiatry, Cornell University Medical School. ix + 312 pages. William Wood & Company, Baltimore. 1935. Price, $4.00.

As the author says, "the study of psychopathology includes such a wide range of topics that it is difficult to select those most pertinent" to the understanding of the nature and causes of personality disorder. He has done well in his selection and in 12 chapters has concisely surveyed the subject. No matter how biased the reader may be, he will find a logical presentation of the factors in the evolution of personality. Sufficient case material is included to clarify his discussion. This book is not as verbose as the usual psychiatric textbook, although the author states that he has written it primarily for medical students and members of the medical profession.

Henry brings out the fact that "in spite of careful and extensive study of functional illness, no pathology of the brain has been disclosed. Furthermore the clinical manifestations of organic psychoses are little more than a caricature of the phenomena observed in functional psychoses. The sequence of emotional stresses which is so important in the evolution of personality disorders is usually irrelevant in organic illness. Just as mental illness is peculiar to human beings, so the associated phenomena would be possible only through the activity of a highly developed cerebral cortex."

The author proves the point that "with failure to take into consideration the psychogenic aspects of illness, not only do physicians make serious errors in diagnosis but their numerous examinations and their discussions at the bedside together with ill-advised medical and surgical treatment may accentuate the illness itself. Even when the physician is alert to these aspects he is inclined to divide the patients into two classes according to whether their illnesses are functional or organic. Such classification is necessarily inaccurate because there are psychogenic elements in all forms of illness, so that in order to understand and to deal effectively with any illness the physician must determine to what extent and under what circumstances psychogenic elements are present." On the other hand "no form of personality disorder offers immunity to physical illness."

In the X and XI chapters the author discusses psychiatric case records and methods of examination. Every physician should read these chapters in order to get some idea of the painstaking effort necessary to proper understanding of human nature. "Snap diagnosis" has no place in scientific medicine.

This is not a book of diagnosis, and the reader will not find listed the clinical entities or any of the various reaction types which occupy the attention of the psychiatrist, but he will find a most readable volume that may well supplement any textbook in medicine or surgery. J. L. McC.

AWARD OF THE JOHN PHILLIPS MEMORIAL MEDAL FOR 1936

DETROIT, MICHIGAN, MARCH 4, 1936

"After careful consideration by the Committee on Awards and upon its recommendation, the Board of Regents of the American College of Physicians has awarded the John Phillips Memorial Medal for 1936 to Dr. Eugene Markley Landis.

"Dr. Landis exemplifies in his training and career and achievements the characteristics which this College wishes to encourage in American medicine and for the honor of which the award of this medal was established.

"Dr. Landis, though young in years, is already old in his experience in the special field of medical research which he has chosen. His contributions to scientific medicine have been numerous and important, and he holds a position of honor among his colleagues which has been recently recognized by his appointment as Assistant Professor in Medicine in the University of Pennsylvania.

"The important contribution of Dr. Landis has been in the field of capillary physiology and of edema. From this his interest has been extended to disturbances of the peripheral circulation, in which field he has made valuable contributions. He has devised new methods for testing these disturbances and for their treatment by a very original device of alternate suction and pressure. More recently he has been active in the study of renal disease in association with Professor Richards.

"It is on the basis of these outstanding achievements that the award of the medal has been made to Dr. Landis, and I have the honor and the privilege, on behalf of the Board of Regents, to bestow upon you, Dr. Eugene Markley Landis, the John Phillips Memorial Medal for 1936."

Presentation address by Dr. James Alex. Miller, President of the American College of Physicians at the Annual Convocation

COLLEGE NEWS NOTES

The following Fellows of the College have become Life Members, making a total of 61 to date:

Dr. Anna Weld, Rockford, Ill.
Dr. Estes Nichols, Portland, Maine
Dr. William H. Watters, Miami, Fla.

GIFTS TO THE COLLEGE LIBRARY

Dr. J. W. Torbett (Fellow), Marlin, Texas—one book, "Pastime Poems of a Busy Doctor." Dr. Torbett's book is autographed "To the Doctors of the American College of Physicians."

Dr. William R. Brooksher (Fellow), Fort Smith, Ark.—one reprint.
Dr. Gerald M. Cline (Fellow), Bloomington, Ill.—one reprint.
Dr. Archibald L. Hoyne (Fellow), Chicago, Ill.—two reprints.
Dr. Manfred Kraemer (Fellow), Newark, N. J.—seven reprints.
Dr. William LeFevre (Fellow), Muskegon, Mich.—one reprint.
Dr. Alfred J. Scott, Jr. (Fellow), Los Angeles, Calif.—one reprint.
Dr. Sidney A. Slater (Fellow), Worthington, Minn.—two reprints.
Dr. Ramon M. Suarez (Fellow), Santurce, P. R.—two reprints.
Dr. John W. Williams (Fellow), Cambridge, Mass.—eighteen reprints.
Dr. Robert B. Wood (Fellow), Knoxville, Tenn.—one reprint.
Dr. Jacob Greenstein (Associate), Providence, R. I.—one reprint.

Dr. Herbert T. Kelly (Fellow), Philadelphia, Pa., was guest speaker, February 5, at the meeting of the Luzerne County Medical Society at Wilkes-Barre, Pa., his subject being "The Early Diagnosis and Treatment of Diabetes."

Dr. Robert B. Radl (Fellow), formerly Physician, Students' Health Service, University of Minnesota, and Assistant Professor in the Department of Preventive Medicine and Public Health, University of Minnesota Medical School, is now associated with the Quain and Ramstad Clinic at Bismarck, N. D.

Dr. John Russell Twiss (Fellow), New York City, Associate in Medicine, New York Post-Graduate Medical School and Hospital, Columbia University, has recently become Assistant Attending Physician, Gouverneur Hospital.

Dr. William C. Voorsanger (Fellow) has been appointed to the Health Advisory Board of the City and County of San Francisco.

Dr. Raymond W. Swinney (Fellow) is chief of the medical staff of the Long Beach Community Hospital and has recently been elected Secretary of the Harbor Branch of the Los Angeles County Medical Society.

Under the Governorship of Dr. L. E. Viko, the Utah members of the American College of Physicians held a sectional meeting at Salt Lake City during the latter part of January.

Under the Governorship of Dr. Adolph Sachs, members of the American College of Physicians held a sectional meeting for the State of Nebraska on January 30, 1936, at Omaha. Dr. Augustus Pohlman, Professor of Anatomy at Creighton University Medical College, addressed the group on "The Physiology of the Lymphatic System." Forty members were present, various committees were appointed and a plan drawn up for meetings each year, alternating between Omaha and Lincoln.

Dr. Albert A. Raymond has resigned from the Rockefeller Institute of Medical Research with which he had been connected for the past nine years to accept the appointment as Director of the Research Laboratories of G. D. Searle & Co., Chicago.

Dr. William D. Weis (Fellow), Crown Point, Ind., is Health Commissioner of Lake County. Lake County is the first and only County in the State of Indiana having an all-time Health Department personnel consisting of the Health Commissioner, Sanitary Inspector, four nurses and a clerk.

The Thirty-Second Annual Congress on Medical Education, Medical Licensure and Hospitals was held at Chicago, February 17 and 18, 1936. Fellows of the College who contributed to the program appear below:

Dr. Walter L. Bierring, Des Moines, Iowa—"Consistency versus Chaos in Medical Education and Licensure."

Dr. James S. McLester, Birmingham, Ala.—"The Personal Characteristics of the Teacher."

Dr. Nathan B. Van Etten, New York, N. Y.—"What Is the Social Objective of the Young Physician?"

Dr. William D. Cutter, Chicago, Ill.—"The Federation and the Survey of Medical Schools."

Dr. Harold Rypins, Albany, N. Y.—"Final Objective—The Federation of State Medical Boards."

Dr. Howard T. Karsner, Cleveland, Ohio—"The Laboratory of Pathology in the Small Hospital."

Dr. W. McKim Marriott, St. Louis, Mo.—"Newer Points of View Concerning the Use of the Outpatient Department in Medical Education."

Dr. Arthur C. Morgan, Philadelphia, Pa.—"Aggressive versus Passive Attitudes of State Board Members."

Other Fellows of the College who participated in the official discussions or as presiding officers included: Dr. Merritte W. Ireland, Washington, D. C.; Dr. Waller S. Leathers, Nashville, Tenn.; Dr. Roscoe L. Sensenich, South Bend, Ind.; Dr. Wilburt C. Davison, Durham, N. C.; Dr. John Wyckoff, New York, N. Y., and Dr. Willard C. Rappleye, New York, N. Y.

Drs. Anthony Bassler (Fellow), Max Einhorn (Fellow) and Samuel Weiss (Fellow) have been selected as the three American physicians who have been named

honorary members of the Belgian Gastroenterological Society. All three are also Fellows of the National Society for the Advancement of Gastroenterology.

Dr. Anthony Bassler (Fellow) has been elected President of the National Society for the Advancement of Gastroenterology, President of the American Committee and United States Delegate to the International Society of Gastroenterology and Vice-Chairman of the Gastroenterological Section of the Pan American Congress.

Dr. Joseph H. Barach (Fellow), Pittsburgh, Pa., has been elected a member of The Society of the Sigma Xi.

ELECTIONS TO FELLOWSHIP

December 15, 1935

Candidates	*Sponsors*
	ALABAMA
James Alto Ward, Birmingham:	William C. Blake, A. B. Craddock, Fred W. Wilkerson.
James Harold Watkins, Montgomery:	C. C. Bass, Philip H. Jones, John H. Musser, Fred W. Wilkerson.
	ARIZONA
Virgil Guy Presson, Tucson:	S. C. Davis, Charles S. Kibler, W. Warner Watkins.
	ARKANSAS
Jesse Dean Riley, State Sanatorium:	F. O. Mahony, George B. Fletcher, Oliver C. Melson.
	CALIFORNIA
Eaton MacLeod MacKay, La Jolla:	Burrell O. Raulston, E. Richmond Ware, F. M. Pottenger, James F. Churchill.
Rudolph Herbert Sundberg, San Diego:	Lyell C. Kinney, C. Ray Lounsberry, James F. Churchill.
Percival Allen Gray, Jr., Santa Barbara:	William D. Sansum, Harry E. Henderson, James F. Churchill.
Robert Ammiel Hare, Santa Barbara:	William D. Sansum, Franklin R. Nuzum, James F. Churchill.
	COLORADO
Ward Darley, Denver:	Clough T. Burnett, James R. Arneill, Gerald B. Webb.
	CONNECTICUT
Robert S. Starr, Hartford:	J. Elder Hutchison, G. Gardiner Russell, Henry F. Stoll.
Samuel Julius Chernaik, New Britain:	C. Brewster Brainard, O. G. Wiedman, Henry F. Stoll.

Candidates	*Sponsors*
William Barclay Terhune, Jr., New Canaan:	C. Charles Burlingame, Francis G. Blake, Henry F. Stoll.
Arthur Hartt Jackson, Washington:	Francis G. Blake, O. G. Wiedman, Henry F. Stoll.
MEDICAL CORPS, U. S. ARMY	
George C. Beach, Fort Leavenworth, Kan.:	Charles R. Reynolds.
Coleridge Livingstone Beaven, Denver, Colo.:	E. L. Cook, William C. Pollock, Charles R. Reynolds.
Samuel McPherson Browne, San Antonio, Tex.:	Charles R. Reynolds.
George Burgess Foster, Jr., Denver, Colo.:	Charles R. Reynolds.
Frederick Hultman Foucar, Washington, D. C.:	Wallace M. Yater, Raymond O. Dart, Charles R. Reynolds.
Arthur Raymond Gaines, Denver, Colo.:	E. L. Cook, William C. Pollock, Charles R. Reynolds.
MEDICAL CORPS, U. S. NAVY	
Clyde Wyndham Brunson, San Pedro, Calif.:	C. S. Butler, Perceval S. Rossiter.
Lyle J. Roberts, Washington, D. C.:	Paul F. Dickens, W. W. Hargrave, Perceval S. Rossiter.
William Wayne Wickersham, Philadelphia, Pa.:	Walter M. Anderson, John H. Chambers, Perceval S. Rossiter.
DISTRICT OF COLUMBIA	
William McCormick Ballinger, Washington:	Wm. Gerry Morgan, Tomás Cajigas, Wallace M. Yater.
John A. Reed, Washington:	William J. Mallory, William A. White, Wm. Gerry Morgan, Wallace M. Yater.
FLORIDA	
Kenneth Phillips, Miami:	William Henry Watters, P. B. Welch, Turner Z. Cason.
ILLINOIS	
Emil Weiss, Chicago:	Isadore M. Trace, Maximilian J. Hubeny, James G. Carr.
Maxim Pollak, Peoria:	William H. Walsh, George Parker, Samuel E. Munson.
Harold Conrad Ochsner, Waukegan:	H. Milton Conner, Arthur E. Mahle, James G. Carr.
IOWA	
Elmer E. Kottke, Des Moines:	John H. Peck, Tom B. Throckmorton, Walter L. Bierring.
KENTUCKY	
Carl Hale Fortune, Lexington:	Charles N. Kavanaugh, John Harvey, Chauncey W. Dowden.
George Earle Wakerlin, Louisville:	J. Murray Kinsman, John Walker Moore, Chauncey W. Dowden.
Benjamin Lane Brock, Waverly Hills:	J. Murray Kinsman, Morris Flexner, Chauncey W. Dowden.

Candidates	*Sponsors*
	LOUISIANA
Thomas Everett Strain, Shreveport:	W. S. Kerlin, T. E. Williams, Joseph E. Knighton.
Clarence Hungerford Webb, Shreveport:	T. P. Lloyd, D. H. Duncan, Joseph E. Knighton.
	MAINE
Edward Alfred Greco, Portland:	Francis J. Welch, John R. Hamel, Edwin W. Gehring.
	MASSACHUSETTS
Gerardo M. Balboni, Boston:	Chester M. Jones, Donald S. King, James H. Means, William B. Breed.
Reginald Fitz, Boston:	Charles F. Martin, James H. Means, Roger I. Lee.
Allen Sheppard Johnson, Springfield:	Laurence D. Chapin, George L. Steele, William B. Breed.
Horace Kimball Richardson, Stockbridge:	Austen Fox Riggs, Sydney R. Miller, James Alex. Miller, William B. Breed.
	MICHIGAN
Harold Riche Roehm, Birmingham:	Walter M. Simpson, Carl V. Weller, James D. Bruce.
Harold Abraham Robinson, Detroit:	William H. Gordon, Henry R. Carstens, James D. Bruce.
	MINNESOTA
Dwight Locke Wilbur, Rochester:	George E. Brown (Deceased), E. V. Allen, Edward L. Tuohy.
Russell M. Wilder, Rochester:	George E. Brown (Deceased), Herbert Z. Giffin, Edward L. Tuohy.
	MONTANA
Ferdinand Ripley Schemm, Great Falls:	Harold W. Gregg, Ernest D. Hitchcock, Louis H. Fligman.
	NEBRASKA
Frank Lowell Dunn, Omaha:	J. A. Henske, John R. Kleyla, Adolph Sachs.
	NEVADA
Lawrence Parsons, Reno:	John C. Ruddock, William H. Leake, Egerton L. Crispin.
	NEW JERSEY
Manfred Kraemer, Newark:	Edward C. Klein, Jr., Lewis W. Brown, Clarence L. Andrews.
	NEW YORK
Max Mensch, Brooklyn:	Philip I. Nash, Thomas J. Longo, Luther F. Warren, Robert A. Cooke.
Samuel Arthur Vogel, Buffalo:	Nelson G. Russell, A. H. Aaron, Allen A. Jones.
Ida J. Mintzer, Jamaica:	Luvia Willard, Marshall C. Pease, Luther F. Warren, Robert A. Cooke.
Robert L. Levy, New York:	Walter W. Palmer, Willard C. Rappleye, Robert A. Cooke.
James Rubeo Lisa, New York:	David S. Likely, Harlow Brooks, Robert A. Cooke.

Candidates	*Sponsors*
Howard Francis Shattuck, New York:	Arthur F. Chace, W. P. Anderton, Robert A. Cooke.
R. Garfield Snyder, New York:	Harlow Brooks, Emanuel Libman, Robert A. Cooke.
	NORTH CAROLINA
George Curtis Crump, Asheville:	A. B. Craddock, Walter R. Johnson, Charles H. Cocke.
William Ray Griffin, Asheville:	Paul H. Ringer, Walter R. Johnson, Charles H. Cocke.
Ronda Horton Hardin, Banner Elk:	Coite L. Sherrill, James W. Vernon, Charles H. Cocke.
Duncan Waldo Holt, Greensboro:	Wingate M. Johnson, J. K. Pepper, Charles H. Cocke.
Jamie W. Dickie, Southern Pines:	P. P. McCain, Paul H. Ringer, Charles H. Cocke.
	OHIO
Frank J. Doran, Cleveland:	Richard Dexter, Edgar P. McNamee, A. B. Brower.
Joseph Marchant Hayman, Jr., Cleveland:	Thomas Fitz-Hugh, Jr., Alfred Stengel, A. B. Brower.
	OREGON
George Wilber Millett, Portland:	John H. Fitzgibbon, Homer P. Rush, T. Homer Coffen.
	PENNSYLVANIA
Ruth Walker Wilson, Beaver:	R. R. Snowden, C. Howard Marcy, E. Bosworth McCready.
Nathan Blumberg, Philadelphia:	Joseph C. Doane, A. M. Ornsteen, E. J. G. Beardsley.
Nathan Harry Einhorn, Philadelphia:	Leonard G. Rowntree, Judson Daland, E. J. G. Beardsley.
Samuel G. Shepherd, Philadelphia:	James E. Talley, Joseph T. Beardwood, Jr., William D. Stroud, E. J. G. Beardsley.
	TEXAS
Earl Jones, Brownwood:	T. C. Terrell, John G. Young, Charles T. Stone.
Henry Franklin Carman, Dallas:	Henry M. Winans, C. M. Grigsby, Charles T. Stone.
	VIRGINIA
Harold Walter Potter, Newport News:	Walter B. Martin, Beverley R. Tucker, J. Morrison Hutcheson.
Wyndham Bolling Blanton, Richmond:	R. Finley Gayle, Jr., Dean B. Cole, J. Morrison Hutcheson.
Douglas Gordon Chapman, Richmond:	Charles M. Caravati, Dean B. Cole, J. Morrison Hutcheson.
	WISCONSIN
Guy Walter Carlson, Appleton:	Otho A. Fiedler, Fredrich Eigenberger, Rock Sleyster.
	CANADA
	Alberta
Percy Harry Sprague, Edmonton:	Albert M. Snell, F. A. Willius, Edward L. Tuohy.

Candidates	*Sponsors*
MEXICO, D. F.	
Fernando Ocaranza, Mexico City:	William D. Nimeh, John J. Sparks, Charles T. Stone.
CHINA	
Mason Pressly Young, Soochow:	P. P. McCain, Edgar A. Hines, Robert Wilson.
SYRIA	
Edward Lewis Turner, Beirut:	Joseph L. Miller, George H. Coleman, Arthur R. Elliott.

ELECTIONS TO ASSOCIATESHIP

December 15, 1935

ALABAMA	
James Bowron McLester, Birmingham:	Groesbeck Walsh, H. Cliff Sauls, Fred W. Wilkerson.
CALIFORNIA	
Bernard Edward McGovern, San Diego:	William Egbert Robertson, Gerald B. Webb, Francis M. Pottenger, James F. Churchill.
Thomas Hodge McGavack, San Francisco:	Dudley W. Bennett, Stacy R. Mettier, William J. Kerr, Hans Lisser.
Edwin Eugene Ziegler, San Francisco:	Marius B. Marcellus, Audley O. Sanders, Hans Lisser, Charles M. Griffith.
COLORADO	
Paul A. Draper, Colorado Springs:	A. Lee Briskman, John A. Sevier, Gerald B. Webb.
Henry Wendell Maly, Colorado Springs:	A. Lee Briskman, John A. Sevier, Gerald B. Webb.
William Corr Service, Colorado Springs:	G. Burton Gilbert, John A. Sevier, Gerald B. Webb.
CONNECTICUT	
John S. Staneslow, Waterbury:	John H. Foster, J. Harold Root, Henry F. Stoll.
Maurice Timothy Root, West Hartford:	J. Elder Hutchison, John A. Wentworth, Henry F. Stoll.
MEDICAL CORPS, U. S. ARMY	
James Brent Anderson, Fort Sam Houston, Tex.:	William H. Allen, Henry C. Coburn, Jr., Charles R. Reynolds.
Forrest Ralph Ostrander, Fort Sam Houston, Tex.:	William H. Allen, Henry C. Coburn, Jr., Charles R. Reynolds.
Stuart Gross Smith, Denver, Colo.:	Everett L. Cook, William C. Pollock, Charles R. Reynolds.
John M. Welch, Washington, D. C.:	Charles R. Reynolds.
Dwight Moody Young, Denver, Colo.:	William C. Pollock, Everett L. Cook, Charles R. Reynolds.
MEDICAL CORPS, U. S. NAVY	
George Arthur Cann, San Diego, Calif.:	Edward C. White, Walter A. Vogelsang, Perceval S. Rossiter.

Candidates	*Sponsors*
U. S. Public Health Service	
Ralph Emmett Porter, Fort Stanton, N. M.:	Meldrum K. Wylder, J. R. Van Atta, LeRoy S. Peters, Hugh S. Cumming.
Thomas Haze Tomlinson, Jr., Fort Stanton, N. M.:	Meldrum K. Wylder, LeRoy S. Peters, Hugh S. Cumming.
District of Columbia	
Frank Stephen Horvath, Washington:	James Alexander Lyon, Tomas Cajigas, Wallace M. Yater.
George Louis Weller, Jr., Washington:	Walter A. Bloedorn, Walter Freeman, William Gerry Morgan, Wallace M. Yater.
Florida	
William Glenn Post, Jr., St. Petersburg:	Roscoe H. Knowlton, Arnold S. Anderson, T. Z. Cason.
Georgia	
Launcelot Minor Blackford, Atlanta:	John B. Fitts, H. Cliff Sauls, Glenville Giddings.
William Howell Kiser, Jr., Atlanta:	John B. Fitts, H. Cliff Sauls, Glenville Giddings.
William Rudy Minnich, Atlanta:	John B. Fitts, H. Cliff Sauls, Glenville Giddings.
Thomas Fort Sellers, Atlanta:	John B. Fitts, H. Cliff Sauls, Glenville Giddings.
Carter Smith, Atlanta:	H. Cliff Sauls, John B. Fitts, Glenville Giddings.
Richard Blanton Wilson, Atlanta:	John B. Fitts, H. Cliff Sauls, Glenville Giddings.
Hartwell Joiner, Gainesville:	John B. Fitts, H. Cliff Sauls, Glenville Giddings.
Illinois	
Clarence J. McMullen, Oak Park:	Hugh A. McGuigan, Arthur E. Mahle, James G. Carr.
Emmet Forrest Pearson, Springfield:	Jacob J. Singer, Alfred Goldman, David P. Barr, Samuel E. Munson.
Iowa	
Richard Oscar Pfaff, Des Moines:	Harry A. Collins, Edward W. Anderson, Walter L. Bierring, Tom B. Throckmorton.
Fred Sternagel, Valley Junction:	John H. Peck, Christian B. Luginbuhl, Walter L. Bierring.
Kansas	
Fred Ernest Angle, Kansas City:	Peter T. Bohan, Howard E. Marchbanks, Thomas T. Holt.
Kentucky	
Marion Foree Beard, Louisville:	J. Murray Kinsman, John Walker Moore, Chauncey W. Dowden.
Max L. Garon, Louisville:	Morris Flexner, J. Murray Kinsman, Chauncey W. Dowden.
Massachusetts	
Thomas Sterling Claiborne, Boston:	Lewis M. Hurxthal, Frank N. Allan, William B. Breed.
Milton James Quinn, Winchester:	Frederick T. Lord, Donald S. King, James H. Means, William B. Breed.

Candidates	*Sponsors*
	MICHIGAN
Bruce Hutchinson Douglas, Detroit:	William A. Evans, Lawrence Reynolds, Charles G. Jennings, James D. Bruce.
David J. Sandweiss, Detroit:	William H. Gordon, Hugo A. Freund, James D. Bruce.
	MINNESOTA
William Arnold Stafne, Moorhead:	George E. Brown (deceased), Bayard T. Horton, Edward L. Tuohy.
Howard Miller Odel, Rochester:	George B. Eusterman, Henry W. Woltman, Edward L. Tuohy.
Martin Van Buren Teem, Rochester:	Bayard T. Horton, Harry L. Smith, Edward L. Tuohy.
	MISSOURI
Hyman I. Spector, St. Louis:	Daniel L. Sexton, Joseph F. Bredeck, David P. Barr, A. Comingo Griffith.
	NEBRASKA
Joseph Daniel McCarthy, Omaha:	Warren Thompson, John R. Kleyla, Adolph Sachs.
	NEW JERSEY
Harold Korb Eynon, Collingswood:	Grant O. Favorite, Dunne W. Kirby, William D. Stroud, Clarence L. Andrews.
Louis Leo Perkel, Jersey City:	Abraham E. Jaffin, Berthold S. Pollak, Clarence L. Andrews.
	NEW YORK
Charles S. Byron, Brooklyn:	Simon R. Blatteis, Henry Joachim, Luther F. Warren, Robert A. Cooke.
Paul Chadbourne Eschweiler, Brooklyn:	Frank Bethel Cross, Joshua M. Van Cott, Robert A. Cooke.
Mendel Jacobi, Brooklyn:	Maurice J. Dattelbaum, Irving J. Sands, Luther F. Warren, Robert A. Cooke.
William August Lange, Brooklyn:	Eugene S. Dalton, Foster Murray, James Alex. Miller, Robert A. Cooke.
Bernard Sternberg, Brooklyn:	David Gingold, Henry Joachim, Luther F. Warren, Robert A. Cooke.
John Josiah Maisel, Buffalo:	George E. Brown (deceased), Fredrick A. Willius, Edward L. Tuohy, Allen A. Jones.
Nelson W. Strohm, Buffalo:	Nelson G. Russell, Carroll J. Roberts, Allen A. Jones.
Alexander Scott Dowling, Corning:	Howard T. Karsner, Carl J. Wiggers, Allen A. Jones.
Harry Clifford Oard, Jamaica:	Carl Boettiger, Ernest E. Keet, Luther F. Warren, Robert A. Cooke.
Louis Ashley Van Kleeck, Manhasset:	Carl Boettiger, Goodwin A. Distler, Luther F. Warren, Robert A. Cooke.
Anthony C. Cipollaro, New York:	Walter G. Lough, David Stanley Likely, Robert A. Cooke.
Julia V. Lichtenstein, New York:	Henry T. Chickering, Carl H. Greene, James Alex. Miller, Robert A. Cooke.
Cornelius Horace Traeger, New York:	Harlow Brooks, Emanuel Libman, Robert A. Cooke.

Candidates	*Sponsors*
	NORTH CAROLINA
Julian Meade Ruffin, Durham:	Paul F. Whitaker, William B. Kinlaw, Charles H. Cocke.
Edward Sandling King, Wake Forest:	Verne S. Caviness, Thurman D. Kitchin, Charles H. Cocke.
	OHIO
Charles S. Greene, Canton:	Joseph H. Barach, Hiram B. Weiss, A. B. Brower.
Dale Pettigrew Osborn, Cincinnati:	Oscar Berghausen, Jacob L. Tuechter, A. B. Brower.
William Orville Ramey, Cincinnati:	David A. Tucker, Jr., John H. Skavlem, A. B. Brower.
Fay Atkinson LeFevre, Cleveland:	Henry J. John, Charles L. Hartsock, A. B. Brower.
Morris Deitchman, Youngstown:	William H. Bunn, Colin R. Clark, A. B. Brower.
	OKLAHOMA
John B. Morey, Ada:	George E. Brown (deceased), Nelson W. Barker, Lea A. Riely.
Ralph Bowen, Oklahoma City:	Henry H. Turner, Lewis J. Moorman, Lea A. Riely.
Homer Albert Ruprecht, Tulsa:	Russell C. Pigford, William J. Bryan, Jr., Lea A. Riely.
	OREGON
Willard Fletcher Hollenbeck, Portland:	John H. Fitzgibbon, Homer P. Rush, T. Homer Coffen.
Merle W. Moore, Portland:	Homer P. Rush, Frank R. Mount, T. Homer Coffen.
	PENNSYLVANIA
Robert Sloan Lucas, Butler:	Jacob C. Atwell, Lester Hollander, E. Bosworth McCready.
Constantine P. Faller, Harrisburg:	Jesse L. Lenker, S. Calvin Smith, E. J. G. Beardsley.
John O. Woods, New Castle:	Wayne W. Bissell, Eliah Kaplan, E. Bosworth McCready.
John Trimble Eads, Philadelphia:	Edward S. Dillon, Samuel B. Scholz, Jr., E. J. G. Beardsley.
Harold R. Keeler, Philadelphia:	Thomas Klein, Charles C. Wolferth, George Morris Piersol, E. J. G. Beardsley.
Charles Fay Nichols, Philadelphia:	Thomas Klein, Russell S. Boles, William D. Stroud, E. J. G. Beardsley.
	RHODE ISLAND
Earl Francis Kelley, Pawtucket:	John F. Kenney, Charles F. Gormly, Alexander M. Burgess.
Russell Stanton Bray, Providence:	Herman A. Lawson, Isaac Gerber, Alexander M. Burgess.
	SOUTH CAROLINA
Francis Eugene Zemp, Columbia:	J. Heyward Gibbes, Hugh Smith, Robert Wilson.
	TEXAS
William Bluford Adamson, Abilene:	Erle D. Sellers, Frederick E. Hudson, Charles T. Stone.

Candidates	*Sponsors*
James John Gorman, El Paso:	Orville E. Egbert, James W. Laws, Charles T. Stone.
Joseph Fielding McVeigh, Fort Worth:	Will S. Horn, Truman C. Terrell, Charles T. Stone.
Edward Randall, Jr., Galveston:	Titus H. Harris, Boyd Reading, Charles T. Stone.
Frances Ralston Vanzant, Houston:	Walter C. Alvarez, George B. Eusterman, Edward L. Tuohy.
William Grady Mitchell, San Angelo:	Albert W. Bromer, Ross V. Patterson, William D. Stroud, E. J. G. Beardsley.
Julian Cox Barton, San Antonio:	Lee Rice, John H. Musser, Charles T. Stone.
William Walton Bondurant, San Antonio:	Lee Rice, Joe Kopecky, Charles T. Stone.
Edgar Marion McPeak, San Antonio:	Lee Rice, Hugh J. Morgan, Charles T. Stone.
David Robert Sacks, San Antonio:	Lee Rice, George R. Herrmann, Charles T. Stone.
	VIRGINIA
James Newton Williams, Richmond:	R. Finley Gayle, Jr., Dean B. Cole, J. Morrison Hutcheson.
	WASHINGTON
Cecil Loveland Morrow, Seattle:	Charles E. Watts, Delbert H. Nickson, Frederick Epplen (deceased).
	WEST VIRGINIA
Dudley Curtis Ashton, Beckley:	J. Morrison Hutcheson, R. Finley Gayle, Jr., John N. Simpson.
Charles B. Chapman, Welch:	Albert M. Snell, James F. Weir, John N. Simpson.
Howard Russell Sauder, Wheeling:	Delivan A. MacGregor, John A. Toomey, John N. Simpson.
	WISCONSIN
Marcos Fernan-Nunez, Milwaukee:	Francis D. Murphy, William J. Egan, Rock Sleyster.
John C. Grill, Milwaukee:	Joseph Lettenberger, Francis D. Murphy, Rock Sleyster.

OBITUARIES

DR. JOHN LEONARD ECKEL

From the Encyclopedia of American Biography we learn that our much beloved confrere, Dr. John Leonard Eckel, who died November 26, 1935, was born in Perrysburg, Ohio, April 28, 1880. He graduated in medicine at the School of Medicine, University of Buffalo, in 1907. He interned at the East Manhattan State Hospital, New York City, and was Junior Assistant Physician there in 1908–09. He held the same post at the Buffalo State Hospital, 1909–10, and was senior assistant physician at the same hospital, 1910–11. September 1911, he went to the University of Berlin and worked in nervous and mental diseases for two semesters under Professors Oppenheim, Ziehn and Jacobson. He also worked in the University of Munich under Professors Alzheimer and Kraepelin. He spent one semester at the University of London, Queen's Square Hospital, for nervous and mental diseases under Professors Gordon Holmes, S. A. K. Wilson, Farquhar, Buzzard, Purves Stewart and Frederick Batten. Returning to Buffalo in 1913, he began a practice limited to nervous and mental diseases and was soon put on the roster of the Medical School of the University of Buffalo. He was Associate Professor of Neurology and Assistant Professor of Psychiatry.

Dr. Eckel went to Vienna for further scientific research and clinical work under Professor Wagner von Jauregg and his assistants, Pappenheim and Schilder. His research work was done with Professor Otto Marburg, Director of the Neuropathological Laboratory. It was there Dr. Eckel's research work " Encephalitis Acutissima " was published in the " Jahrbuch " in January 1926. This was an outstanding bit of work which was widely quoted, referred to and favorably mentioned in European medical journals. He did much research work with Dr. N. W. Winkelman of the University of Pennsylvania and Temple University, Philadelphia, going to Philadelphia every month for over 15 years. Several of the most valuable articles he wrote were in collaboration with Dr. Winkelman.

Dr. Eckel was attending and consulting neurologist and psychiatrist to the Buffalo General Hospital, Millard Fillmore Hospital, Memorial Hospital, Our Lady of Victory Hospital, Buffalo City Hospital, Sister's Hospital, Providence Retreat, Crippled Children's Guild, Emergency Hospital and J. N. Adam Memorial Hospital at Perrysburg, N. Y.

He was a member of the American College of Physicians, The Buffalo Academy of Medicine, Erie County and New York State Medical Societies, American Medical Association, American Psychiatric Association, American Neurological Association, American Association for Research in Nervous and Mental Diseases, New York Neurological Society, Philadelphia Neurological Society, Central Neuro-Psychiatric Association, Buffalo

Neuro-Psychiatric Society, Pan-American Medical Association and the American Association for the Advancement of Science and held important offices in many of these organizations.

Dr. Eckel was asked to read papers at the following meetings: the British and American Neurological Societies, London, July 28, 1927; the First International Congress on Neurology in Berne, Switzerland, September 3, 1931; the Pan-American Medical Congress in Dallas, Texas, May, 1933; the Pan-American Floating Congress, March, 1934; the Second International Congress on Neurology in London, August 1, 1935, etc.

During the World War, Dr. Eckel held the commission of Captain in the U. S. Army.

He was a member of the Saturn Club, the University Club, the Buffalo Club, the Torch Club and many other social and fraternal organizations.

John Leonard Eckel had personal charm of manner which won many friends. He was sound in his work and practice and thorough in his clinical approach, possessed of a sunny nature with a winning smile and presence, comforting to the sick, yet, withal, inspiring confidence and trust.

His death was almost a tragedy. He apparently did not realize he was ill but had precordial and epigastric pain a few days before his sudden death. He went, however, to see some of his patients and while sitting beside one of them while two nurses stood by, according to the account given in the *Courier-Express*, "he straightened in his chair, sighed and died."

ALLEN A. JONES, M.D., F.A.C.P.,
Governor for Western New York.

DR. HENRY FINLAY HYNDMAN

Dr. Henry Finlay Hyndman (Associate), Wichita, Kansas, died on October 31, 1935, of diabetes mellitus; aged, 49 years.

Dr. Hyndman was born in Adrian, Illinois, May 4, 1886. He received the degree of Bachelor of Arts from the University of Kansas, in 1908, and the degree of Doctor of Medicine from the Medical School of that institution in 1910.

Dr. Hyndman devoted his practice to internal medicine but was especially interested in diabetes. He was a member of the staff of St. Luke's Hospital, Wellington, Kansas, 1911–18; member of staff, Wichita Hospital, 1918 to date; chief of service and member of Executive Council of the staff of Sedgwick County Charity Hospital of Wichita, from 1933 to date; and a member of the medical service and President of Staff of Wesley Hospital, Wichita, from 1929 to date. He was a member, also, of the Sedgwick County Medical Society, Kansas State Medical Society, Nu Sigma Nu Fraternity, a Fellow of the American Medical Association, and had been an Associate of the American College of Physicians since December 16, 1934.

"Dr. Hyndman stood for and practiced the highest principles in his profession. He loved his work and was unwaivering in his endeavor to live up to the professional code of ethics. He was never heard to speak disparagingly of any colleague's work or character. Basically he was one of that group of disappearing physicians—the family doctor. Of recent years, however, he devoted most of his time to the care of diabetics and was one of the foremost men in this type of work in Kansas. . . . Our Society has lost an enthusiastic and progressive member and we all have lost a dear friend, and a counsellor."—Medical Bulletin of The Sedgwick County Medical Society.

DR. WILLIAM KRAUSS

Dr. William Krauss (Fellow), Meridian, Miss., died December 21, 1935, in the Gartly-Ramsay Hospital, Memphis, of carcinosis originating in x-ray burns of the hand; aged, 74 years.

Dr. Krauss was born in Bavaria. He graduated from the Memphis College of Pharmacy in 1883. He then attended the Memphis Hospital Medical College, graduating in 1889. He pursued postgraduate study in histology, pathology and bacteriology at the University of Kiel and at the University of Wurzburg. He was successively Assistant in Anatomy, Instructor in Chemistry, Histology, Pathology and Bacteriology at the Memphis Hospital Medical College between 1890 and 1903. He became Dean and Professor of Pathology in the Medical Department of the University of Mississippi, 1909–10, after having served as Professor of Pathology and Tropical Medicine in the College of Physicians and Surgeons, Memphis, 1906–09. From 1912 to 1929, he was Professor of Tropical Medicine at the University of Tennessee College of Medicine. He was at one time Secretary of the Board of Health of Memphis; also, acting Assistant Surgeon in the U. S. Public Health and Marine Hospital Service, serving as diagnostician during the yellow fever epidemic in 1897–98 and in 1905. At one time he was Director of Laboratories, Memphis City Health Department, and just previous to his death had been with the Stingily Laboratories, Meridian, Miss., in the capacity of Director of the x-ray department and of the laboratories proper.

Dr. Krauss was a past President of the Memphis and Shelby County Medical Society; a past President of the West Tennessee Medical and Surgical Association; a member of the Mississippi State Medical Society; Southern Medical Association and the American Medical Association.

At various times he served on the staffs of the Memphis General, Baptist and St. Joseph's Hospitals, all of Memphis. He was a former Chairman of the National Malaria Commission and Chairman of the Tennessee Pellagra Commission. Dr. Krauss became a Fellow of the American College of Physicians during 1919.

DR. GEORGE WASHINGTON McCASKEY

Dr. George Washington McCaskey (Fellow), Fort Wayne, Ind., died December 30, 1935, of cerebral hemorrhage and cerebral arteriosclerosis; aged, 82 years.

Dr. McCaskey was born at Delta, Ohio, graduated from the Jefferson Medical College of Philadelphia in 1877 and began practice in Fort Wayne, Ind., in 1882. He became an outstanding diagnostician and was nationally known as an authority on diseases of the stomach. For a number of years he served as professor of the theory and practice of medicine in the old Fort Wayne Medical College. He was professor emeritus of medicine at the Indiana University School of Medicine in Indianapolis.

Dr. McCaskey was a member and past president of the Indiana State Medical Association, a member and past president of the northern Tri-State Medical Association, a member of the American Medical Association, the American Gastro-Enterological Association and had been a Fellow of the American College of Physicians since June 5, 1917. He was the author of more than one hundred publications.

DR. STEPHEN R. PIETROWICZ

Stephen R. Pietrowicz, a Fellow of the College since 1920, died January 12, 1936. Dr. Pietrowicz was born in Posen, Poland, August 23, 1873. He attended St. Mary Magdalene Gyminazium, Posen, Poland. In his young manhood he came to America where he continued his education at St. Stanislaus College, Chicago, and at the College of Physicians and Surgeons of Chicago, School of Medicine, University of Illinois, from which he received his medical degree in 1898.

Since that time he was engaged in practice in Chicago, for many years devoting special attention to internal medicine. He was attending physician at St. Mary's of Nazareth Hospital in Chicago from 1900 to 1908; physician-in-chief of the same hospital from 1908 to 1925; and president of the staff and senior attending physician from 1925 to the time of his death.

He served as attending physician at Cook County Hospital from 1911 to 1913. He was superintendent of the Chicago State Hospital in 1912. From 1911 to 1917 he was senior professor of medicine at the Chicago College of Medicine and Surgery. From 1918 to 1920, associate in medicine, University of Illinois. Thereafter, until the time of his death he was clinical professor of medicine, Loyola University School of Medicine.

He was a member of the school board of Chicago at one time. He held membership in the Society of Internal Medicine of Chicago; the Institute of Medicine, Chicago; the Chicago Medical Society; Illinois Medical Society; American Medical Association; Chicago Pathological Society; Polish Medical Society; Chicago Tuberculosis Institute.

Through many years Dr. Pietrowicz carried on a very busy and extensive practice. He gave much of his time to his work in the hospital and medical school. His interest in St. Mary's of Nazareth Hospital was especially great and he rendered a service which will long be remembered. Deeply interested in his life work, he gave himself without stint to those who came under his care.

JAMES G. CARR, M.D., F.A.C.P.
Governor for Northern Illinois.

DR. CHARLES CRAWFORD HINTON

Dr. Charles Crawford Hinton (Fellow), Macon, Georgia, died suddenly of coronary artery disease on February 25, 1936, aged 47.

Dr. Hinton was born at Milledgeville, Georgia, October 1, 1888. He attended the public schools of Bibb County and entered Emory University, now at Atlanta but then at Oxford, Georgia, graduating with the degree of B.Ph. in 1909. He thereafter entered the medical department of Johns Hopkins University School of Medicine, graduating in 1913. His internship was spent in a Baltimore hospital, whereupon he became Assistant in Medicine and Chief of the Out-Patient Department Clinics of Emory University. In 1916 he became Associate in Medicine at Emory University, remaining until 1917. From 1919 until the time of his death, he was Laboratory Consultant to the U. S. Veterans Administration at Macon, and from 1920 until the time of his death, he was Internist to the Middle Georgia Sanatorium. He was a former president of the Macon Medical Society of Bibb County, a member of the Southern Medical Association, the American Medical Association and the Clinical Society of Middle Georgia Sanatorium. He had been a Fellow of the American College of Physicians since 1929.